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A NEUROPSYCHIATRIC AND GENETICAL INVESTIGATION OF ACUTE INTERMITTENT PORPHYRIA

By LENNART WETTERBERG

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BY

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SVENSKA BOKFÖRLAGET/Norstedts

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PREFACE

I wish to convey my respectful appreciation to Professor Hans Forssman, director of the Psychiatric Research Centre, Ulleråker Hospital during 1961—1964, the temporary director Associate Professor Mats Gruvstad 1964—1966 and the present director Professor Lars-M. Gunne and Professor Jan A. Böök, director of the Institute for Medical Genetics who provided the scientific atmosphere as well as the research facilities necessary for my work.

The comprehensive and thorough investigation of acute intermittent porphyria in Sweden, which has been carried out by Professor Jan Waldenström since the early 1930s, provides a wealth of information on the biochemistry, epidemiology, genetical etiology and clinical variations of this disease. I am greatly indebted to Professor Waldenström for his generosity in placing his accumulated family data at my disposal which greatly facilitated my work.

I am also much indebted to Assistant Professor Birgitta Hæger-Aronsen, Malmö for valuable assistance in standardizing the biochemical methods and in the collection of supplementary family data.

I am indebted to Mrs. Daga Falk for excellent genealogic work and Miss Christina Östlund for skilful technical assistance. Moreover, I wish to thank all colleagues in the different hospitals in Sweden for allowing access to the hospital records of their patients and for permitting me to include these cases in my study.

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INTRODUCTION

Acute intermittent porphyria (AIP)[1] is characterized by variable clinical symptoms, mainly gastro-intestinal and neuro-psychiatric, and the occasional appearance of red urine which becomes dark on standing (Waldenström 1937). The most conspicuous gastro-intestinal disorders are pain of colic type, vomiting, constipation and diarrhea. The neurological symptoms vary but pareses of irregular types are common. Anxiety, confusion, hallucinations and sleep disturbances may lead to admission to a psychiatric hospital where the patient, if the true nature of his condition is not understood, may be given barbiturates which may cause alarming symptoms, such as respiratory paralysis. The first clinical manifestation of this disease occurs usually between 20 and 40 years of age. Females are more often affected than males in a ratio 3: 2.

The psychiatric manifestations occur only in some patients with acute intermittent porphyria but not in others. The association between AIP and mental illness might alternatively be explained as (1) due to random combinations of AIP and mainly non-genetical conditions, (2) combinations of AIP and independent genetical psychiatric conditions, or (3) the consequence of the occurrence of AIP having somatic as well as psychiatric manifestations.

These tentative explanations, which do not cover all possible alternatives, were taken as working hypotheses.

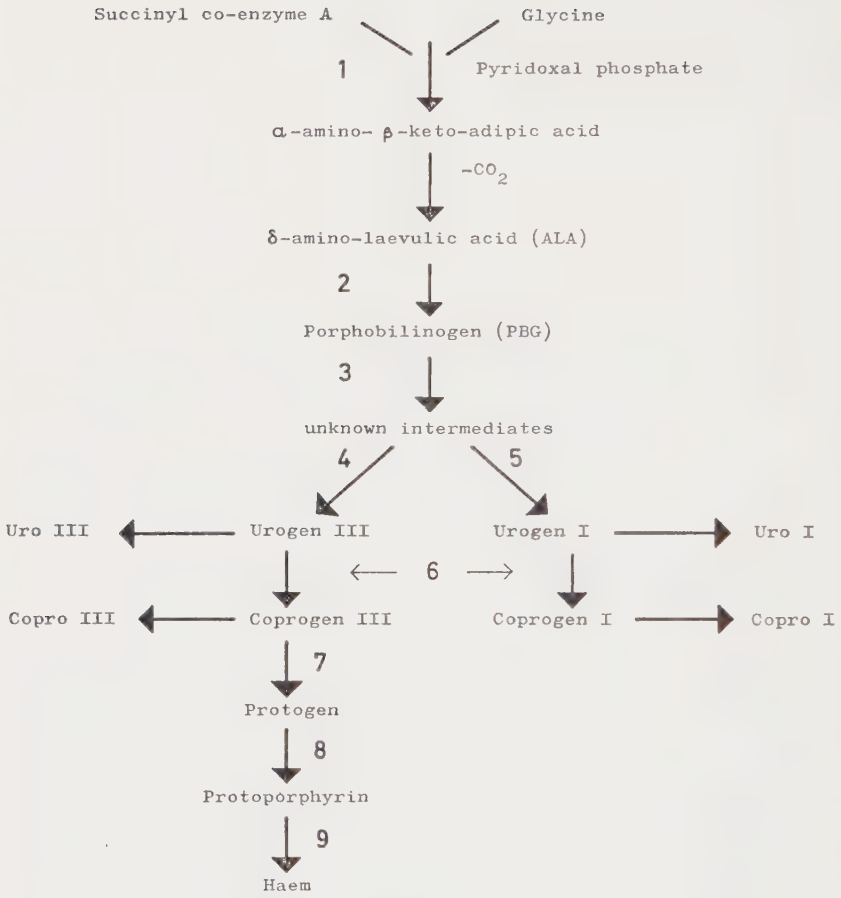
To test these different hypotheses a genetical investigation of a sample of Swedish families with AIP was carried out.

[1] Abbreviations used: AIP, acute intermittent porphyria; ALA, δ-aminolaevulic acid; PBG, porphobilinogen.

I. ERRORS OF PORPHYRIN METABOLISM

The hereditary nature of the disorders of porphyrin metabolism was first appreciated by Günther (1912, 1922) and by Garrod (1923) who considered them to belong to the group of "inborn errors of metabolism". Waldenström (1934, 1935, 1936, 1937, 1939, 1956, 1957) named these disorders of metabolism *porphyrias,* and presented extensive evidence that the etiology of the acute hepatic form is basically genetical. Engel and Wallquist (1935) described a pedigree with AIP from North Sweden. Further investigations on AIP in Sweden have been carried out by Waldenström and Hæger-Aronsen (1963, 1964, 1967).

Normal porphyrin biosynthesis. The first step in porphyrin biosynthesis (cf. Fig. 1) is the condensation of succinyl co-enzyme A and glycine activated by pyridoxal phosphate (Shemin and Kumin 1952, Shemin and Russell 1953, Wriston *et al.* 1955, Schulman and Richert 1955, 1957, Granick 1958, Kikuchi *et al.* 1958) and ferrous ions (Brown 1958). The product of this reaction, α-amino-β-ketoadipic acid rapidly forms δ-aminolaevulic acid (ALA). This reaction occurs in the mitochondria and is catalyzed by the enzyme ALA-synthetase (Gibson 1958, Gibson *et al.* 1962, Burnham and Lascelles 1963). The condensation of ALA to form porphobilinogen (PBG), the monopyrrole precursor of porphyrins, is catalyzed by ALA-dehydrase (Cookson and Rimington 1953, Dresel and Falk 1953, Granick 1954, Gibson *et al.* 1955, Schmid and Shemin 1955, Lascelles 1959, Tschudy *et al.* 1962, Labbe and Onisawa 1962, Burnham and Lascelles 1963). PBG is converted to uroporphyrinogen in man in a way that is not completely understood. Russeli (1967) has proposed a condensation of PBG with a linear tripyrryl-methane to form uroporphyrinogen III. In other species two enzymes are known to be involved in the production of uroporphyrinogen, a heat-stable deaminase and a heat-labile isomerase both of which act on postulated intermediate polymers to form uroporphyrinogen III



1 δ-aminolaevulic acid synthetase
2 δ-aminolaevulic acid dehydrase
3 Porphobilinogen deaminase
4 Porphobilinogen isomerase
5 Porphobilinogen deaminase
6 Uroporphyrinogen decarboxylase
7 Coproporphyrinogen decarboxylase
8 Protoporphyrinogen oxidase
9 Heme synthetase = Ferrochelatase

Fig. 1. Schematic presentation of the pathway of porphyrin biosynthesis. Uro = uroporphyrin; Urogen = uroporphyrinogen; Copro = coproporphyrin; Coprogen = coproporphyrinogen; Protogen = protoporphyrinogen.

from PBG (Booij and Rimington 1957, Bogorad 1958 a, b, c, Bogorad and Marks 1960). Uroporphyrinogen decarboxylase converts the uroporphyrinogen to coproporphyrinogen which enters the mitochondria, where it is converted to protoporphyrin (Granick and Mauzerall 1958, Sano and Granick 1961, Porra and Falk 1961, 1964). This reaction may involve several steps. It is postulated that protoporphyrinogen is oxidized to protoporphyrin by protoporphyrinogen oxidase (Porra and Falk 1964). The incorporation of ferrous ions into protoporphyrin to form heme is facilitated by the enzyme heme synthetase or ferrochelatase (Goldberg *et al.* 1956, Goldberg 1959, Labbe 1959, Lockhead and Goldberg 1959, Labbe and Hubbard 1960, Porra and Jones 1963 a, b).

Classification of porphyrias

The fact that the exact nature of the biochemical disturbance is still unknown makes classification of human porphyria difficult (Waldenström and Hæger-Aronsen 1967). The porphyrias can, however, be divided into two main forms (Schmid *et al.* 1954), the erythropoietic and the hepatic porphyrias. In the erythropoietic group the porphyrins and porphyrin precursors are increased in the bone marrow, but in the hepatic form in the liver. The acute intermittent type of porphyria investigated in this study belongs to the hepatic porphyrias. A number of classifications have been proposed for the hepatic porphyrias, but none has been universally accepted. The classification proposed by Waldenström and the synonymous terminologies from other systems of classification are presented in Table 1. The opinions of the classification and nomenclature of the different porphyrias differ in particular with reference to the cutaneous manifestations (*i.e.* group II—IV in Table 1). The topic was discussed during a recent international conference on the porphyrias (Rimington 1963).

Waldenström (1957) has pointed out that the term acute porphyria is misleading since the metabolic defect is chronic even if there are attacks of the acute type. Furthermore he suggested that the term porphyria should be dropped in favor of pyrrolia since the disease is known to have a disturbance in pyrrol metabolism.

In correspondence with the diagnosis porphyria cutanea tarda (PCT), the diagnosis of the acute hepatic form would be porphyria acuta inter-

Table I. Classification of hepatic porphyrias according to Waldenström and Hæger-Aronsen (1967). Synonymous terminology in parentheses.

I	Acute intermittent porphyria, (pyrroloporphyria, Swedish type of porphyria).
II	Porphyria cutanea tarda hereditaria.
III	Porphyria cutanea tarda symptomatica (symptomatic porphyria, urocoproporphyria, constitutional porphyria).
IV	Porphyria variegata, (protocoproporphyria, mixed porphyria, South African genetic porphyria).

mittens (PAI) a term which has sometimes been used (Waldenström and Hæger-Aronsen 1963). The term acute intermittent porphyria (AIP) first suggested by Schwartz and Watson (1942) is, however, so well established in the literature that its use will be continued in the present work. Dermatological manifestations are rare in AIP at least as it appears in Sweden (Waldenström 1957), and no patient has been reported to have displayed cutaneous symptoms of the type usually found in the South African genetic porphyria.

The excretory patterns of porphyrins and their precursors in urine and feces in different types of hepatic porphyria is shown in Table 2. The main biochemical lesions of AIP and their differential diagnostic characteristics are discussed later (page 13) where details of the table are further clarified.

The classification of the porphyrias is based on biochemical and clinical observations. It has not yet been established whether the different clinical entities have their counterparts in specific genetical entities.

Reviews of the various types of porphyria found in different parts of the world have been published, *e.g.* from Sweden by Waldenström (1937, 1957), Hæger-Aronsen (1963) and Waldenström and Hæger-Aronsen (1963, 1967), from England by Goldberg and Rimington (1962), from France by Gajdos and Gajdos-Török (1962), from South Africa by Eales (1961) and Dean (1963), from Denmark by With (1963), and from the United States by Watson (1964).

Biochemical changes in acute intermittent porphyria

Increased quantities of PBG are excreted in the urine both during acute attacks and in remissions (Sachs 1931, Waldenström 1937, Vahlquist

Table 2. Concentration of δ-aminolaevulic acid (ALA), and porphobilinogen (PBG) in urine, and of coproporphyrin (CP) and protoporphyrin (PP) in feces of individuals with different types of porphyria. (After Hæger-Aronsen, 1963.)

Type	Stage	Urine		Feces	
		ALA	PBG	CP	PP
Acute intermittent porphyria	Acute	**	***	*	*
	Latent / Remission	(*)	**	*	*
Porphyria cutanea tarda hereditaria or symptomatica	Acute	(*)	N	**	*
	Latent / Remission	N	N	***	**
Porphyria variegata	Acute	**	***	***	***
	Latent / Remission	(*)	(*)	***	**

(*) to *** = increased. N = Normal.

1939, Mauzerall and Granick 1956) (cf. Table 2). In addition, many patients excrete large amounts of ALA at least during acute attacks (Mauzerall and Granick 1956, Hæger 1958). The concentration of uroporphyrin of freshly voided urine may be within normal limits (Cookson and Rimington 1954). A sporadically occurring increase in the amount of uroporphyrin in the urine could be caused by condensation of PBG to uroporphyrin, a process which has been observed in vitro (Waldenström and Vahlquist 1939, Westall 1952, Cookson and Rimington 1953, 1954). The excretion of copro- and protoporphyrin in the feces is only slightly increased (Hæger-Aronsen 1962), in contrast to the large amounts excreted by patients who have the South African form of acute porphyria (Dean and Barnes 1959, Eales *et al.* 1966).

High amounts of ALA-synthetase has been found in patients with acute porphyria, as well as in experimental animals intoxicated by porphyria-inducing chemicals (Granick and Urata 1963, Granick 1963, 1966, Tschudy *et al.* 1965, Nakao *et al.* 1966). The response of the liver to such chemicals is to synthesize enzymes that "detoxify" the substance (Brodie and Maikel 1961, Conney and Burns 1963). One of these mechanisms is hydroxylation of aliphatic groups of aromatic rings, ac-

complished by mixed functions of oxidases which among others requires heme. Granick (1966) using the regulator-operator hypothesis of Jacob and Monod (1961), postulated that in acute human porphyria a mutation has occurred in an operator gene so that its activity is repressed, inefficiently, by the repressor. This repressor requires heme to be able to inactivate the operator gene, *i.e.* to reduce ALA-synthetase production. If now the heme is displaced from the aporepressor by a chemical inducer the operator becomes active, ALA-synthetase is produced and porphyrins and heme are formed.

In acute intermittent porphyria the symptoms as well as the biochemical abnormalities seldom appear before puberty (Waldenström 1957, Hæger 1958). This indicates a connection with the sex steroids (Welland 1964, Granick 1966, Zimmerman *et al.* 1966), which occasionally may provoke acute attacks in some individuals *e.g.* in women taking oral contraceptives (Redeker 1963, Wetterberg 1964, Dean 1965). Oral progestational agents have been reported to be apparently successful in preventing the appearance of symptoms in four women with AIP (Hæger-Aronsen 1963, Perlroth *et al.* 1965). The production of ALA-dehydrase has been shown by Russell and Coleman (1963) to be genetically controlled in inbred strains of mice. The same authors also found that ALA-dehydrase was high in the mouse fetal liver, fell to a low level shortly after birth and rose again to the adult level at three to six weeks of age. No studies are known concerning the hepatic level of ALA-dehydrase in man at various ages. In an adult with acute porphyria, reported by Nakao *et al.* (1966), the liver ALA-dehydrase activity was twice that of a control individual.

Some of the biochemical abnormalities reported in patients with porphyria may be secondary to the primary genetic lesion, and some of those observed in experimentally produced porphyria in animals by different compounds, such as sedormid and griseofulvin, are almost certainly not related to the genetically controlled forms. Abnormalities of glycine metabolism have been demonstrated in human acute porphyria (Richards and Scott 1961), but not as a constant phenomenon. Barbiturates which may be deleterious to patients with AIP (Waldenström 1937, 1957) have structural similarities with compounds known to induce porphyria in animals (Cowager *et al.* 1962), and inhibit oxidative phosphorylation in vitro (Aldridge and Parker 1960).

Abnormalities of tryptophane metabolism have been reported together

with a functional pyridoxine deficiency (Druyan and Hæger-Aronsen 1966, Elder and Mengel 1966, Hamfelt and Wetterberg 1967). Disturbances of lipid metabolism (Schwartz 1955), thyroid function (Hellman *et al.* 1963), iron metabolism (Kramer 1963), amino acid metabolism (Mellinkoff *et al.* 1959, Druyan *et al.* 1965) and an inappropriate secretion of antidiuretic hormone (Hellman *et al.* 1962, Ludwig and Goldberg 1963, Nielsen and Thorn 1965, Perlroth *et al.* 1966) are some other occasional conditions reported in AIP-patients.

Further studies of the biochemical lesions in AIP have been summarized by Watson (1964), Tschudy (1965), Rimington (1966) and Schmid (1966).

The clinical manifestations show preference for certain abdominal and neurological symptoms which may reflect non-randomized target areas in the nervous system, although the link between such lesions and the observed disturbance in porphyrin synthesis is unknown. The clinical symptoms apparently are not correlated with the excreted amount of ALA and PBG (Ackner *et al.* 1961). In fact, the excretion may be higher in asymptomatic individuals than in patients with clinical manifestations.

During an acute attack of porphyria psychotic symptoms, sometimes of a schizophrenic type, may occur (Waldenström 1937, Peters 1962). This observation may be of interest for research on the etiology of psychotic states in general.

Psychiatric manifestations

The first extensive investigation of AIP was reported by Günther (1911, 1922) who noted abdominal pain, constipation, vomiting and psychiatric disturbances as the prominent symptoms in the disease he referred to as Hämatoporphyrie. Waldenström (1937) made a clinical survey of 103 cases of acute porphyria in Sweden. Five of these cases had been admitted to mental hospitals because of psychotic manifestations and about 20 cases displayed other mental symptoms.

In 1954 Markovitz reported five cases of AIP and reviewed an additional 64 cases reported between 1941 and 1953. Mental changes had been observed in 80 per cent of these patients, and in 14 per cent they were the initial symptoms of the attacks. Minor changes such as irrita-

bility, tiredness or restlessness were noted in 40 per cent. Fifty-two per cent of the patients had hallucinations, delirium, confusion or seizures. In 26 per cent the patients had a diagnosis of hysteria, schizophrenia, depression or "paranoia". Markovitz also remarked that "the irritability, noisiness and demanding attitude of these patients made them difficult to manage. Three of our five patients left the hospital against medical advice".

Psychiatric manifestations in AIP patients have been reported after Markovitz' review 1954 among others by Cross (1956), von Reis (1958), Duret-Cosyns and Duret (1959), Eilenberg and Scobie (1960), Holmberg (1961), Kaelbling *et al.* (1961), Keeler (1962), Godlewski (1963 a, b), Frazier (1963) and Hennessy (1963).

Of 50 cases reported by Goldberg and Rimington (1962) twenty-nine had mental symptoms. The symptoms were grouped in order of increasing severity as follows, (1) depressed, nervous, hysterical, lachrymose or "peculiar"—(14 cases), (2) confused, hallucinating, disoriented or with personality changes—(9 cases), and (3) legally certified—(6 cases).

Peters (1962) described about 100 cases with abnormal porphyrin metabolism obtained by intensive screening of admissions to neurological and psychiatric departments. About half of the patients had mental symptoms which were similar to those in toxic psychoses, *e.g.* bizarre behaviour, catatonic-like excitement, misidentification, déjà vu phenomena, auditory and sometimes visual hallucinations resembling those of acute delirium tremens. Peters suggested that a schizophrenic porphyric syndrome may exist since in his material over a dozen patients displayed a schizophrenia-like psychosis as the only or predominant manifestation. Moreover, these psychoses did not differ from classical schizophrenia either by Rorschach test or independent psychiatric evaluation. Rowland (1961) studied the neurologic and psychiatric aspects of the disease, particularly with respect to possible enzymatic defects. He pointed out that any theory of the pathogenesis of AIP will have to explain the long latent period prior to the onset of symptoms in adult life, the intermittent nature of the symptoms and the role of exogenous factors such as barbiturates.

The literature on psychogenic factors in AIP was reviewed by Ackner *et al.* (1962) in connection with a report of a neuropsychiatric investigation of 13 cases. In these cases psychiatric symptoms commonly occurred during an acute attack of porphyria. Ackner *et al.* were of the opinion

that the symptoms were unrelated to the underlaying metabolic defect if the diagnosis was not assisted by electroencephalographic findings. They found neither evidence in support of psychogenic etiology of the mental disorders, nor neurotic predispositions in the family nor predisposing pre-morbid personality variations in the patients.

II. DEFINITIONS OF DIAGNOSTIC CRITERIA FOR THIS INVESTIGATION

The following diagnostic criteria for acute intermittent porphyria and operational definition of mental illness were used in this investigation.

Acute intermittent porphyria

1. Increased excretion of porphobilinogen (PBG) in the urine, measured per gram creatinine as well as per ml urine according to the method of Mauzerall and Granick (1956). In addition, the extinction curve of the Ehrlich reacting substance had to show a typical PBG-pattern with maxima at 525 and 555 nm in tests from at least one urine sample from each case.
2. Increased amounts of δ-aminolaevulic acid (ALA) in the urine was considered as further evidence of AIP, while other chemical examinations were considered as inconclusive.

Individuals, whose tests satisfied these biochemical criteria but lacked symptoms of clinical disease were classified as *latent* cases of AIP. Patients who in addition to their positive biochemical tests as explained above had at any time displayed the characteristic signs or symptoms of abdominal and/or neurological types were classified as *manifest* cases of AIP. The abdominal symptoms recorded as characteristic were: pain of spastic type, vomiting, constipation and diarrhea, and the neurological signs and symptoms were: tremor, akathesia, parkinsonism, cephalalgia, paralysis, paraesthesia, muscular asthenia, hypotonic and atonic reflexes, atrophies of the muscles, diplopia, amaurosis or seizures. Relatives with negative biochemical AIP tests, irrespective of their symptoms, have been considered as *non-affected*. When groups of relatives are referred

to as having AIP or being affected, manifest as well as latent forms have been included unless stated otherwise.

Mental illness

All individuals who displayed at least three of the following seven symptoms without regard to the duration of the condition, were classified as mentally ill:

1. Confusion
2. Hallucinations or illusions
3. Depression
4. Prominent suicidal thoughts or attempts
5. Anxiety
6. Certain types of emotional disturbances (apathy, ambivalence, depersonalization and immaturity)
7. Insomnia.

These different symptoms have been defined in the following way.

1. *Confusion*

Confusion was defined as a disturbance of consciousness characterized by impairment of the sensorium, by difficulties in grasping, and by bewilderment, perplexity, disorientation, disturbances of associative functions, and poverty of ideas (Noyes and Kolb 1958).

2. *Hallucinations and illusions*

Hallucinations and illusions are both disorders of perception. In illusions, a real object forms an image symbol which is misinterpreted. Hallucinations occur in the absence of external stimulation when images originate from processes taking place in the central nervous system and are experienced as external real phenomena. It is often impossible to decide

which one of the two different forms of perceptional disorder is actually present (Riss 1959). When details were available it was noted whether the disorder was of the auditory, visual, olfactory, gustatory or tactile type.

3. *Depression*

Depression was defined as a feeling of sadness associated with an unpleasant feeling of tension. Efforts are generally accompanied by mental pain, the patient looses his normal initiative and becomes restrained in a feeling of hopelessness which is reflected in his attitude and behaviour. He is unable to make important decisions and experiences difficulties in daily routine mental activities. Only conditions which limit the patient's normal daily activity considerably have been registered as depressions.

4. *Prominent suicidal thoughts or attempts*

In addition to verified attempts to commit suicide, preoccupation with suicidal thoughts as mentioned spontaneously or during questioning in interviews with the patient, or noted as causing concern to his relatives or associates, were recorded under this heading.

5. *Anxiety*

Anxiety was defined as a state of increased, disruptive nervous tension, combined with a feeling of uneasiness, apprehension, frustration and restlessness. Anxiety was registered when of such a degree as to interfere with the patient's routine activities.

6. *Certain types of emotional disturbances*

The symptoms were recorded and defined in the following way: *apathy* as dullness or absence of emotional response to pleasant or painful experiences; *ambivalence* as emotional indecision caused by contradictory feel-

ings towards the same object; *depersonalization* as a feeling of unreality experienced either as a change of the patient's own personality or as a transposition to an alien world; *immaturity* as dependency on the environment often expressed in a childish and dramatic way and a demand for immediate gratification of wishes.

7. *Insomnia*

Insomnia was recorded provided it was of some permanence and causing the patient concern.

III. BIOCHEMICAL IDENTIFICATION OF ACUTE INTERMITTENT PORPHYRIA

This section describes the biochemical methods which were used in this work and their standardization based on a sample of healthy individuals. For an appreciation of the influence of drugs on the outcome of the biochemical tests, urine samples from mental hospital patients receiving various medications were investigated. Finally, all available individuals belonging to the family material were tested.

Various endogenous factors which may interfere with the determination of PBG are urobilinogen (Sachs 1931, Waldenström 1937), indole derivatives (Waldenström 1937, Dalgliesh 1952, Ludwig 1958) and urea (Vahlquist 1939, Prunty 1945). Watson *et al.* (1964) found several exogenous factors: phenazopyridine hydrochloride, methyl-red, beet pigment, skatol red and certain melanogens which gave a pseudo-Ehrlich reaction, and might lead to an erroneous diagnosis of acute intermittent porphyria. The Watson-Schwartz test (1941) is probably most frequently used for the qualitative determination of PBG in urine mainly because it is economical and rapid. In the great majority of the cases of manifest acute intermittent porphyria, the Watson-Schwartz test is sufficient (Watson *et al.* 1964) and it has been considered to be the only economically feasible method available for large scale screening tests (Kaelbling *et al.* 1961). Comparisons of the findings for ten different series of patients screened for urinary PBG are summarized in Table 3, which includes the methods used, the composition of the population sample and country in which the procedure was performed, the number of cases examined, and the number with positive PBG reactions. In some of the screening procedures, the positive reactions were inconclusive because reexaminations with other methods were lacking or not informative.

Due to its higher specificity, the more time-consuming method of Mauzerall and Granick (1956) was preferred in this work.

Table 3. Summary of ten screening procedures for porphobilinogen in the urine.

Year	Authors	Method	Population sample	No. of cases	No. of positive reactions
1948	Hammond *et al.*	W—S	mixed from general hospital (USA)	1000	none
1957	Markovitz	W—S	epileptics (USA)	91	47
1959	Berman *et al.*	Ehrlich	epileptics on barbiturates (Czecho-Slovakia)	769	none
1961	Kaelbling *et al.*	W—S + M—G	mentally ill (USA)	2500	35; 12 manifest, 9 latent, 1 mixed, 13 secondary
1962	Peters	W—S + M—G	mental or neurological (USA)	un-known	almost 100
1964	Sasaki *et al.*	W—S	with symptoms like AIP (Japan)	261	6, 2 AIP 12 pesudo-reaction
1964	Townsend	W—S modification	mixed patients (USA)	1000	none
1965	Anguiano *et al.*	Ehrlich	mentally ill males (Mexico)	80	48
1965	Scott	W—S	epileptics (England)	93	none
1965	Jancar *et al.*	W—S	epileptics (England)	122	3

W—S = Watson-Schwartz' method (1941).
M—G = Mauzerall and Granick's method (1956).

Determination of δ-aminolaevulic acid (ALA) porphobilinogen (PGB) and creatinine in the urine

ALA and PBG were determined according to the method of Mauzerall and Granick (1956), which includes purification of urine on ion-exchange resin columns.

Creatinine in the urine was determined by the method of Jaffe (1886).

Standardization of methods on a sample of apparently healthy individuals

Normal values for ALA, PBG and creatinine in human urine were determined in samples from apparently healthy individuals of the Ulleråker Hospital staff, 50 males and 50 females, aged 20 to 55 years. All the analyses were performed on freshly voided samples, usually of morning urine.

The creatinine value was determined so that the ALA and PBG excretion could be corrected for the varying concentrations of the different urines (Hæger 1958). The mean value of the urinary excretion of creatinine, expressed as mg per 100 ml urine, was 159 ± 77 (S. D.). Since no significant differences were found between male and female excretions of ALA and PBG, the groups were pooled (Table 4). All values exceeding the mean plus two standard deviations have been regarded as pathological in the present work. For ALA the upper borderline value was 0.76 mg per 100 ml urine and 4.6 mg per gram creatinine. The corresponding values for PBG were 0.33 and 1.8.

Precision of the method

The standard error of the method was calculated from double determinations of 50 urine samples. They were chosen within the range of the upper borderline values for ALA and PBG given ALA concentrations between 0.00 and 0.82 mg per 100 ml and PBG concentrations between 0.00 and 0.44 mg per 100 ml. It was found to be:

Table 4. Urinary excretion of δ-aminolaevulic acid (ALA) and porphobilinogen (PBG) in 100 human control cases.

Substance	δ-aminolaevulic acid		Porphobilinogen	
in mg	Mean	S.D.	Mean	S.D.
Per 100 ml urine	0.34	0.21	0.17	0.08
Per gram creatinine	2.40	1.10	1.20	0.32

1. for ALA
   0.04 mg per 100 ml urine or
   0.26 mg per gram creatinine
2. for PBG
   0.02 mg per 100 ml urine or
   0.17 mg per gram creatinine.

Instability of δ-aminolaevulic acid and porphobilinogen

ALA is stable only under certain conditions. Urine can be stored at +4° C in the dark at pH levels between 4 and 7 for at least 3 weeks without much decrease of the concentration of ALA (Hæger-Aronsen 1960). However, PBG is unstable at room temperature and more so if not protected from daylight (Waldenström and Vahlquist 1939). If it is necessary to store the urine before analysis of PBG it should be done at a pH of about 7—8 (alkalinized with sodium carbonate) (Hæger-Aronsen 1960).

The instability of PBG in human urine samples was studied under the following light exposure and temperature conditions. Urine samples from ten porphyric patients were used. The initial concentration of PBG varied between 0.83 and 6.5 mg per 100 ml and the pH ranged from 5 to 7 for the 10 samples. Each sample was divided into 40 portions of 1 ml each. Ten portions were kept at +22° C in the dark, ten at +22° C but not protected from daylight, ten in the dark at +4° C and ten

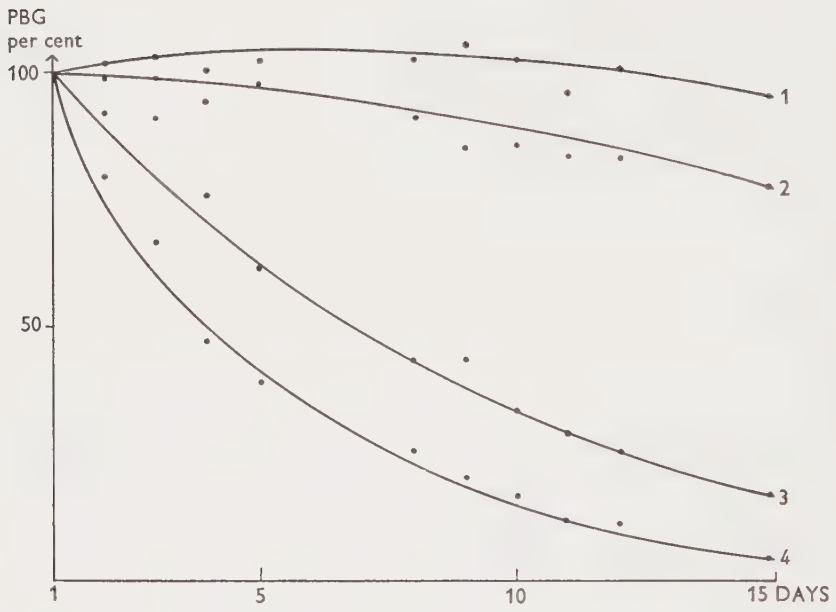


Fig. 2. Stability of PBG in urine samples from ten patients with AIP. The values are mean values expressed as per cent of initial concentration calculated to 100 per cent. Samples kept in the dark, 1: at $-25°$ C, 2: at $+4°$ C, 3: at $+22°$ C, and not protected from daylight, 4: at $+22°$ C.

portions in the dark at $-25°$ C. Portions from each storage condition were examined on 10 occasions within a period of 14 days for changes in the concentration of PBG.

There was a rapid decrease in concentration of PBG when the urine was allowed to remain at room temperature and exposed to daylight (cf. Fig. 2). Urine can be stored at $-25°$ C in the dark for at least 2 weeks without any apparent fall in the concentration of PBG and for one week in the dark at $+4°$ C without much decrease. For determination of PBG, all transportations of urine samples at room temperature must be rapid and the samples should be protected from light.

The daily decrease in PBG concentrations at $+4°$ C and $+22°$ C in individual urine samples cannot be calculated from Fig. 2, and used to extrapolate the initial concentrations, since the concentration, the pH changes in different storage conditions and other factors may influence

the stability of PBG. Investigation of the significance of such variables was not carried out because it was not possible to control these different factors before transportation of the urine, when it was sampled by the patients themselves.

False reactions found in a sample of mental hospital patients

Urine specimens from 1907 patients (1039 males and 868 females) at two mental hospitals in northern Sweden were examined. All patients, who were in the ward on the day of urine collection were included in the study. Samples of fresh morning urine specimens from about twenty patients per day were sent to Uppsala by air in plastic bottles, stored in thermo bags at + 10° C. Before transportation the pH of the specimens was adjusted to between 7 and 8 by addition of sodium carbonate. In most cases only a small amount of sodium carbonate or none had to be added. No other preservatives were used. The urines were analysed no later than the day after they had been collected.

Of the 1907 patients in the two mental hospitals, 170 (9 per cent) were found to have abnormally high amounts of PBG or a substance reacting like PBG in their urines. While most of the urines contained moderately increased amounts of the compound corresponding to 2 to 5 mg PBG per gram creatinine, it was above 10 mg in 4 cases.

It was possible to reexamine 73 of those urines and the compound reacting with Ehrlich reagent was characterized in each case with an extinction curve. In three cases the urinary compound showed the typical extinction curve for PBG with maxima at 525 and 555 nm whereas in the remaining 70 cases there was a flat curve with a plateau around 560 nm. The reacting compound of these 70 urines did not show the typical pink-to-red colour but instead had a green-blue tint, which darkened within a few hours after exposure to daylight. Furthermore unlike PBG the substance showed a blue fluorescence in UV light.

Urinary excretion of ALA was normal in these 70 cases, also indicating that the diagnoses AIP must be questioned since about 2/3 of all cases with AIP were reported to have increased urinary excretion of ALA (Hæger 1958).

For further evaluation of the AIP diagnosis, all 170 patients with increased amounts of the reacting compound in the urine, were examined with regard to symptomatology, age, diagnosis and medication on the day of urine sampling. In each of the two hospitals 100 control cases, 50 males and 50 females were selected at random from the patients with normal amounts of PBG in their urine. These 200 patients, hereafter called the control group, as well as the 170 patients with abnormally high amounts of PBG or a PBG-like substance were compared for the factors under consideration. Their medical records showed no evidence that any of the 170 patients had AIP, except for the three cases with proved increased urinary excretion of PBG.

The main difference between the two groups was that large amounts of phenothiazine derivatives had been given to the 170 patients. Of these 128 (75 per cent) received more than 200 mg phenothiazines daily as compared to 7 of the 200 patients in the control group. It was therefore hypothesized that the compound reacting with Ehrlich reagent may be derived from the phenothiazines administered. The nature of the substance is not yet elucidated, but investigation on this problem is in progress (Reio and Wetterberg 1967).

After the observation that a urinary compound in some mental patients induced an error when Mauzerall and Granick's method was used for determination of PBG, the additional requirement for verification of PBG was an extinction curve of the typical PBG pattern with the two maxima at 525 and 555 nm for all Ehrlich reacting urines with extinction above the upper limit when read at 555 nm.

Porphyrin precursors in the parents and siblings of forty patients with acute intermittent porphyria

Urines from 225 members of 40 families with acute intermittent porphyria, selected for the genetic and psychiatric study (cf. page 35), were examined. The analyses of the urine were usually carried out on samples of morning urine. For the hospitalized patients the samples were stored at + 4° C in the dark until they were analysed. The family members who were in their homes were asked to send specimens of morning urine, which were to be collected in plastic bottles without preservatives and

Table 5. Urinary excretion of porphobilinogen (PBG), expressed as mg per gram creatinine, in 197 siblings of 40 sibships, divided into three groups according to the presence of acute intermittent porphyria (AIP).

Form of AIP	No. of cases	Mean	S.D.
Unaffected	89	1.04	0.76
Latent	32	18.0	24.0
Manifest	76	32.0	29.0

mailed to Uppsala where the analyses were made, most of them the day after and all within two days after the collection of the urine. The pH was between 5 and 7 for most of the specimens at that time. During the field study (see page 36) the urine specimens were collected when I visited the patient. If the results of the first determination of PBG were not conclusive for the diagnosis of AIP, *i.e.* the amount of PBG was increased either when measured per gram creatinine or per ml urine, additional specimens were examined when obtainable.

Of the 225 members of the 40 family sample, 197 were siblings (including eight half siblings) in 40 sibships, and 28 were parents. Of the 197 siblings 108 (55 per cent) showed increased excretion of PBG in their urine and were classified as having AIP and 89 were considered as not affected. Clinical evaluation of the affected siblings showed that 76 had the manifest form and 32 the latent form af AIP. The results of the determinations of urinary excretion of PBG in the different groups are found in Table 5. The manifest cases excreted an average of 32.0 mg PBG per gram creatinine in their urine and the latent cases 18.0 mg.

The amounts of urinary excretion of PBG did not differ between the A-*propositi, i.e.* 20 AIP patients with mental illness and the B-*propositi, i.e.* 20 patients with AIP only (cf. page 35). Three cases, all females, *i.e.* case 1:3, 2:1 and 36:4 (the first figure indicates the family number and the second the rank in the sibship, as recorded in the appendix), excreted more than 100 mg PBG per gram creatinine; each had been treated in a mental hospital and had been disabled for a period by neurological signs and symptoms of AIP.

In nine siblings (4.5 per cent) the excretion of urinary PBG was

Table 6. Urinary excretion of δ-aminolaevulic acid (ALA), expressed as mg per gram creatinine, in 197 siblings of 40 sibships, divided into three groups according to the presence of acute intermittent porphyria (AIP).

Form of AIP	No. of cases	Mean	S.D.
Unaffected	89	2.4	1.3
Latent	32	11.0	17.0
Manifest	76	15.0	15.0

between 1.8 and 2.9 mg per gram creatinine (*i.e.* pathological) but less than 0.33 mg PBG per 100 ml urine (*i.e.* normal). Under physiological conditions PBG is reabsorbed in the tubuli, but in AIP an "overflow" of the metabolite has been demonstrated (Druyan *et al.* 1965). A possible renal defect as the cause of a borderline excretion of PBG in the nine siblings was not found. However, examinations of renal function and determination of a 24-hour urinary output of PBG under standardized conditions were lacking for practical reasons. Consequently the nine siblings were classified as un-affected with AIP according to the diagnostic criteria for AIP used in this investigation (cf. page 18).

The results of the excretion of ALA in the urine are given in Table 6. The mean for the manifest cases was 15.0 mg ALA per gram creatinine and for the latent cases 11.0. Seventy-seven of the 108 patients with AIP were found to have pathological amounts of urinary ALA excretion. The three manifest cases with the largest amount of ALA in their urine are the same patients having the largest amount of PBG.

Case 25: 6, with latent AIP excreted 15 mg PBG and 97 mg ALA per gram creatinine although he did not show any symptoms of AIP, not even when he had on one occasion received large doses of barbiturates in major anesthesia.

The youngest member of the family sample, a boy 13 years old (38: 4), excreted 9.1 mg ALA per gram creatinine (*i.e.* above upper limit), but normal amounts of urinary PBG, 1.0 mg per gram creatinine. He was classified as non-affected by AIP, but since he had experienced acute attacks of gastro-intestinal disturbances of porphyria type he may still have AIP, although it had not yet become biochemically manifest. With

(1967) found that some members of the porphyria families he investigated showed increased urinary excretion of ALA in spite of normal amounts of PBG and he considered those patients to have the gene for porphyria and to represent a subclinical form of porphyria. Such cases are considerably rarer in the 40 Swedish families than in the Danish sample. Furthermore, the risk in confusing AIP with lead intoxication makes an increase of urinary ALA excretion, an as yet unacceptable, single criterion for the diagnosis of AIP.

Two cases were found to occasionally excrete abnormal amounts of PBG. When their urines contained an increased amount, the reacting substance was found to show the typical PBG extinction curve. Such intermittent excretors can only be diagnosed by repeated tests. According to Hæger-Aronsen (1963) they are infrequent and she states that if the urinary PBG is normal, the risk of latent AIP is very small.

IV. GENETICAL INVESTIGATION

The majority of the genetical interpretations derived from analyses of family and pedigree data, or from *propositi* with manifest AIP have been based, so far, on apparently more or less inadequate and biased samples. Even so it is reasonable to accept the explanation of heterozygosity for a rare single autosomal dominant gene as the genetical determinant of AIP in the majority of the affected individuals.

The proportion of siblings affected with manifest AIP to non-affected siblings falls short of the expected 1:1 ratio but apparently healthy siblings may have a latent form, *i.e.* positive PBG urine tests. If the latent cases are counted as "affected" a better fit is obtained. The error of porphyrin metabolism can be identified in practically all of the manifest cases by measuring urinary PBG. The efficiency of identifying 'carriers' *(i.e.* the latent forms) of the dominant mutation with the PBG urine test is also presently estimated at almost 100 per cent for adults having the Swedish type of AIP (Hæger-Aronsen 1963).

Inasmuch as it can be assumed that a family sample from Sweden is likely to be genetically more homogeneous than, for example, a similar family sample in the United States, and because most of the AIP patients in Sweden are restricted to a limited number of pedigrees (Waldenström 1956) it was anticipated that a Swedish family sample would provide data relevant to the present problem. On the other hand, such a sample could not be expected to contribute much further to the analysis of the genetical transmission other than a confirmation of the already claimed simple dominant inheritance (Waldenström 1937, 1956).

The major problem, however, on which the interest, from a genetical viewpoint, was focused, concerned the association between AIP and mental illness. It is well known that psychiatric manifestations, varying from acute confusional states to moderate or mild depressions occur in some AIP patients but not in others. Such associations might be explain-

ed alternatively as (1) due to random combinations of a specific genetical entity (AIP) and mainly non-genetical reactive conditions, (2) the result of random or selective combinations of AIP with independent genetical psychiatric conditions or (3) the consequence of the occurrence of one or possibly several specific AIP mutations more or less regularly causing somatic as well as psychiatric manifestations (*i.e.* pleiotropism). A specially designed genetical analysis should provide some evidence for or against these schematized hypotheses or other possible alternatives.

A comparison was made of the occurrence and associations of AIP (latent and manifest forms) and psychiatric illnesses between the siblings of (A) a sample of *propositi* displaying AIP as well as mental illness and (B) a sample of *propositi* displaying AIP but without evident mental illness.

According to the first hypothesis one would not expect any consistent differences between the two groups of relatives. On the basis of the second, the A-*propositi* would be selected for two independently segregating mutations which as a consequence would segregate independently among their relatives. The incidence of the psychiatric condition among the relatives of the B-*propositi*, on the other hand, should correspond to its incidence in the general population.

Finally, with the third alternative those relatives of the A-*propositi* who were affected with AIP (latent or manifest) should also develop, frequently or consistently, psychiatric manifestations similar to those of the A-*propositi* whereas the B-relatives with AIP should display a random assortment of psychiatric conditions as expected from the epidemiological situation of the general population to which they belong.

To provide the necessary factual information for a discussion of the three alternative hypotheses outlined above, a randomized sample of a total of 40 families (*i.e. propositi*, their parents and siblings) was estimated to be reasonably sufficient and practical for a follow up investigation with personal interviews and examinations of every available family member. The 40 families consisted of two equal groups, one in which the *propositi* had AIP as well as mental illness and another group in which the *propositi* displayed the signs and symptoms of AIP, only.

Ascertainment of the data

Registration of propositi and their families

The family sample was obtained in the following way.

A fairly complete registration of AIP in Sweden was achieved through combined longitudinal and cross-sectional casefinding surveys. The large material of porphyria investigated by Waldenström up to 1957 was complemented by a systematic inquiry into all relevant hospital admissions which were on record (Hæger-Aronsen 1958). For the present investigation an additional inventory was undertaken in early 1965 and this new registration covered admissions during the period 1958 to 1964 inclusive.

As a result of the inventories a total of 708 cases (272 men and 436 women) were identified of whom 461 (174 men and 287 women) were still living in late 1964. From these 461 patients a total of 100 were selected randomly for the sample (cf. Table 7). The addresses of the 100 patients were traced by means of the parish registers which sometimes also contained information on admissions to mental hospitals.

Further information about hospitalization and other types of medical care was obtained through questionnaires sent to the patients. The patients' records from the respective sources were requested and scrutinized. Five cases were excluded because a diagnosis of AIP could not be verified. The data concerning these five cases follow.

1. Woman, 28 years old in 1964, diagnosed as AIP with hypochondria. About five years of intermittent attacks of abdominal pain and at the same time she often presented a red urine and consequently the diagnosis AIP was considered. In addition she was of a "hysteric constitution", and this may have been one of the reasons why the possibility of other somatic disorders was not fully appreciated. She also displayed symptoms of transvestism, which was interesting as she had a normal twin sister, from whom she was separated at the age of two when she was adopted and then lost contact with her biological family. The patient was admitted to the Research Centre at Ulleråker Hospital for verification of the diagnosis of AIP. The first day in the clinic she complained of severe pain localized on the left side of the abdomen and radiating to the left groin. Roentgenogram showed a stone in the region of the left kidney and by operation a stone consisting mainly of calcium oxalate was removed. After the operation the urine did not show any red colour. She excreted normal amounts of ALA and PBG

even after provocation by glycine ad modum Richards and Scott (1961). Thus the diagnosis of acute intermittent porphyria could not be verified.

2. Woman, 38, with intermittent abdominal pain, bronchial asthma and periods of depression; treated several times in a mental hospital. The patient, the mother and three siblings had normal urinary excretion of ALA and PBG which excludes AIP, according to the criteria of the present investigation.
3. Woman, 49, with relatives in whom AIP had been diagnosed. In the five years previous to examination she had displayed symptoms of epilepsy, depression and intermittent abdominal pain. She was treated several times with electroconvulsive therapy and barbiturates were given as premedication. At one time she was sent to a hospital for barbiturate intoxication but without any sign of the deleterious pharmacogenetic effect often noted in patients with AIP. She was admitted to the Research Centre at Ulleråker Hospital and provocation with glycine ad modum Richards and Scott was made but the investigation did not reveal any disturbed metabolism of ALA or PBG and the diagnosis AIP was excluded.
4. Man, 49, abdominal pain of unknown origin diagnosed on different hospital admissions as lumbago-ischias, spastic colitis and jejunitis. At one time the diagnosis of acute intermittent porphyria was considered mainly because of the multiple abdominal disturbances though without biochemical verification of AIP. Since he excreted normal amounts of ALA and PBG, he diagnosis acute intermittent porphyria was excluded.
5. The fifth patient was not available for a follow up examination and was therefore excluded.

The remaining 95 patients in whom the diagnosis of acute intermittent porphyria was verified were divided into two groups:

(I) patients with AIP and mental illness — 23
(II) patients with AIP, only — 72.

From each of these two groups 20 patients were selected at random to serve as index cases or *propositi* (a summary of the procedure for selecting the 40 *propositi* is found in Table 7). The 40 families selected in this way comprised a total of 328 individuals including 40 *propositi*, 80 parents and 199 full and 9 half sisters and brothers. *Propositi* as defined under (I), their families and individual family members have been given the prefix A-, *i.e.* A-*propositi*, A-families etc. Correspondingly, the prefix B- is used with reference to *propositi* as defined under (II) and their families (cf. Table 9).

Table 7. Procedure for selecting a random sample of 40 patients with acute intermittent porphyria (AIP) who were registred as *propositi* for the genetical analysis.

Swedish patients with AIP	No. of patients
All cases registered at the end of 1964	708
All cases living at the end of 1964	461
Random sample selected for personal examinations	100
Number of patients from the above 100 sample for whom genuine AIP was confirmed	95
Patients from the above group of 95 who displayed AIP *as well as* mental illness (*i.e. propositus* sample I)	23
Patients from the above group of 95 who displayed signs and symptoms only of AIP, (i.e. *propositus* sample II)	72
Group A *propositi* (selected from sample I)	20
Group B *propositi* (selected from sample II)	20

Field investigation

A personal field investigation was carried out from September 1965 to September 1966 for the purpose of visiting and examining the 227 living members of the 40 family sample. The addresses and dates of birth for the parents and the siblings of the *propositi* were obtained from the parish register offices. For the 101 deceased members information on date of death was included.

Most of the family members returned questionnaires with information about their previous and current health condition and dates and place when they had consulted a doctor or were admitted for hospital care. Histories of hospital admissions were checked and complemented by personal studies of available records whenever possible. Of the 227 living members 223 were interviewed by myself, 210 by personal examination, 11 by telephone and two by letter. Two were interviewed by helpful colleagues. It was not possible to reach two individuals who had lost contact with their families. One of them had emigrated to the United States.

The personal interviews of the family members followed a prepared form. The different items included personal and family history, individual medical history, social condition and state of health and illnesses,

Table 8. Age distribution in 1964 of 149 living full siblings of the 40 A- and B-*propositi* (cf. page 35) with acute intermittent porphyria.

Age	A-siblings		B-siblings	
(years)	Males	Females	Males	Females
10—19	—	1	3	2
20—29	5	1	7	1
30—39	8	8	11	4
40—49	14	11	7	3
50—59	12	13	5	9
60—69	1	2	9	8
70—79	—	—	2	2
Totals	40	36	44	29

Mean age for A-siblings 44.4 ± 10.3 (S.D.)
Mean age for B-siblings 46.8 ± 16.2 (S.D.)

respectively, of other family members. With few exceptions, the patients and their relatives were interviewed in the privacy of their homes.

On the same occasion urine samples were secured for PBG and ALA analyses.

Acute intermittent porphyria

The initial genetical analysis will deal with AIP irrespective of its associations with mental symptoms and as identified by its characteristic clinical features and/or by chemical identification (*i.e.* including latent cases). For this purpose all 40 families can be pooled.

In these 40 sibship-parent combinations, which include two marriages between first cousins, there are 23 female and 17 male *propositi* with a mean age of 42 years when registered for this investigation. The total number of individuals in the 40 families was 328. Fifty-one parents had died by 1964 and 28 were living. One sibling (15: 8) and one parent (1: F) were not available for examination. Nine half siblings included in other parts of this work were excluded from the genetical analysis. Of the remaining 198 full siblings 149 were living. The age distribution of these 149, 76 A- and 73 B-siblings is shown in Table 8. There was

Table 9. Distribution of 199 full siblings of A-*propositi* (AIP with mental illness) and B-*propositi* (AIP without mental illness). Complete observations available for 167 siblings to classify them as affected [manifest acute intermittent porphyria (AIP) and latent form (aip)] and unaffected. The remaining 32 siblings could not be diagnosed at time of the present investigation because they were under age of onset (< 15 years), deceased or had moved.

Families	Examined living sibs over 14 years of age and deceased with hospital AIP diagnosed						Disappeared by the time of the present investigation or under 15 years of age					
	Affected				not affected		0—14		15—40		> 40	
	AIP		aip									
	M	F	M	F	M	F	M	F	M	F	M	F
A1—A20	11	15	9	8	24	16	11	6	2	1	1	—
B21—B40	9	15	12	3	27	18	4	4	2	1	—	—
Totals	20	30	21	11	51	34	15	10	4	2	1	—

no difference between the means of age of the A- and B-siblings ($P > 0.05$).

The average age of onset, defined as the age at the time of the first diagnosed acute attack, for the 40 *propositi* was 29 years. A summary of the family data is given in Table 9.

Sex distribution

Of the 50 siblings with AIP in its clinically manifest form, 20 were males and 30 females. A further 32 siblings were diagnosed as having the latent form, only, and of these 21 were males and 11 females.

The sex ratio of the latent cases has been reported to be the same as that of the manifest cases, 2 males to 3 females (Hæger-Aronsen 1963). If the sex distribution of the 32 latent cases in the present family material is compared with that of all living patients with AIP registered in Sweden in 1964, *i.e.* 461 cases (174 males and 287 females), the sex distribution differs significantly ($P < 0.01$).

Assuming that manifest and latent AIP represent different degrees, only, of the manifestations of the same gene mutation adding the two categories of cases gives a distribution of 41 males and 41 females.

The sex distribution of the same form of AIP among the parents completely investigated was, 3 fathers with manifest AIP of 15 affected, compared to 10 of 16 mothers affected (cf. Table 11).

The most likely explanation of the finding that both sexes are equally affected with AIP, is a mutation which can be identified at two different levels. This would imply that for some as yet unknown genetical and/or environmental reasons females are less protected against the deleterious effects of this mutation. An inquiry into this mechanism may well add important information leading to adequate therapeutic measures.

Karyotype

Gonosomal deviations, probably of incidental nature, have been found in three patients with AIP (Hambert and Wetterberg 1964, Nielsen 1966). Chromosomal analyses of cultured leucocytes from two randomly selected AIP-patients of this material, one of each sex, have been carried out (by courtesy of Professor Jan A. Böök). Both patients had normal karyotypes.

Birth rank

The rationale, in this context, of testing the distribution of the 40 *propositi,* in respect to birth rank in their respective sibships, is that a random distribution favours the interpretation of a genetical etiology. Non-random distributions, on the other hand, are more likely to have environmental implications.

As seen from Table 10, the birth ranks of the 40 *propositi* did not differ significantly from those expected on the basis of random distribution. Six patients were first-born and 12 last-born, figures which do not differ significantly from the expected number of 8.6. Twenty *propositi* belonged to the first half and 20 to the second half of the birth series. Of the secondary cases, a category which includes latent as well as manifest AIP, 44 belonged to the first and 38 to the second half of the series.

The data lend no support to the assumption that factors connected with either the mother's age at the birth of the child, or the number of pregnancies, are of significance in the occurrence of acute intermittent porphyria.

Table 10. Distribution of 40 *propositi* with acute intermittent porphyria (AIP) by birth rank.

Sibship size	Birth rank of *propositi*													Expected no. each rank
	1	2	3	4	5	6	7	8	9	10	11	12	13	
1	(1)													—
2	2	1												1.50
3	3	2	4											3.00
4	1	—	1	2										1.00
5	—	1	1	—	—									0.40
6	—	4	—	—	—	2								1.00
7	—	1	—	—	—	—	—							0.14
8	—	1	—	3	—	1	—	1						0.75
9	—	—	—	—	—	1	1	—	1					0.33
10	—	—	—	1	—	—	—	—	—	1				0.20
11	—	—	—	—	—	—	—	—	—	1	—			0.09
12	—	—	—	—	—	—	—	—	—	—	—	—		—
13	—	—	1	—	—	—	—	1	—	—	—	—	—	0.15
Observed total	6	10	7	6	—	4	1	2	1	2	—	—	—	39
Expected total	8.6	8.6	7.1	4.1	3.1	2.7	1.7	1.5	0.8	0.4	0.2	0.2	0.2	39
			Firstborn 6							Lastborn 12				

χ^2 for heterogeneity = 1.2
DF = 3
$0.80 > P > 0.70$

Analysis of family data

Sufficient information was available for 28 sibships about both parents to infer definitely, or with some assurance, whether they should be diagnosed as affected (latent and manifest AIP) or not affected. As seen in Table 11, 31 out of the 56 parents were affected. Subtracting the three sibships, in which the data indicated that both parents were affected, we obtain for the remaining 25 sibships exactly one affected parent per sibship. This is what is to be expected if all carriers of a single heterozygous mutation can be identified by the applied diagnostic techniques. Such results imply that penetrance is complete with respect to an identifiable metabolic error but also that manifestation may occur at different

Table 11. Manifest (AIP) and latent (aip) acute intermittent porphyria. Distribution of affected and unaffected completely investigated parents of 28 *propositi* with manifest AIP.

Parents (n = 56)	Affected		Total affected	Not affected
	AIP	aip		
Fathers	3	12	15	13
Mothers	10	6	16	12
Totals	13	18	31	25

levels and with more or less deleterious consequences for the individual carrier of the mutation.

The 40 *propositi* had a total of 199 full siblings (150 living and 49 deceased by 1964). Altogether 25 siblings had disappeared from observation before, or were under the age of 15. The can be disregarded since the beginning of the manifestation period for the clinical as well as the latent form of AIP is approximately at the age of 15 (Waldenström 1957, Hæger 1958). In an extensive material of some 600 Swedish AIP-cases (Waldenström and Hæger-Aronsen 1967) only five cases had their first clinical manifestation of the AIP-disease before the age of 15. Assuming that the upper limit for the age of onset is at 40 years (Waldenström 1957), there are six individuals (cf. Table 9) who disappeared while still in the risk zone and one after the age of 40. Complete observations are available for 167 siblings. The application of a correction by Weinberg's abridged method (Weinberg 1925) would add only 4.0 to this sum and the lack of information for 7 individuals was therefore considered immaterial.

The 40 sibships were divided into three groups according to the nature of the available information about the parents:

a. Twenty-five sibships with conclusive evidence of one affected (latent or manifest) and one unaffected parent.
b. Three sibships with one affected and one very likely affected parent, *i.e.* probable matings between two heterozygotes (or carriers).
c. Twelve sibships with inadequate information about one or both parents and who were not available for biochemical investigations.

Table 12. Manifest (AIP) and latent (aip) forms of acute intermittent porphyria. Distribution of affected and unaffected individuals in sibships of *propositi* with manifest AIP by type of parental mating.

Parental combinations	No. of sibships	Affected				Total affected	Not affected		
		AIP		aip			M	F	Totals
		M	F	M	F				
(a) ▲ × △	25	12	17	11	4	44	33	22	55
(b)* ▲ × $\overset{?}{▲}$	3	3	6	4	3	16	3	3	6
(c)* $\overset{?}{△}$ × $\overset{?}{△}$	12	5	7	6	4	22	17	12	29

▲ affected; △ not affected; $\overset{?}{△}$ inconclusive information; $\overset{?}{▲}$ probably affected.

* including one marriage between first cousins.

The distribution of affected and non-affected individuals in these three groups of sibships, evaluated in accordance with Weinberg's *propositus* method, is presented in Table 12.

The ratio affected/non-affected in group (a) is 44: 55 and in group (c), 22: 29. For both groups the ratios are in statistical agreement with the 1:1 ratio expected from a mating between one individual with a heterozygously expressed single gene mutation and another homozygous for the corresponding normal alleles.

The three sibships of group (b) show a ratio of 16 affected to 6 unaffected which lends some support to the initial interpretation that both parents were affected. Children of two heterozygotes (carriers) would stand a risk of 75 per cent of developing alternatively the latent or the manifest form of porphyria. Of the 3 (b) group families (*i.e.* **8**, **14** and **15**) 73 per cent of the siblings were affected. This means that some of them may have been homozygotes. There was no evidence of abortions or still births in these families. Possible homozygote siblings could not be differentiated from heterozygote siblings *e.g.* by more extreme expression of AIP.

The slightly lower than expected number of affected siblings in groups (a) and (c) may, of course, depend on false negative results of the biochemical tests (including possible periodically negative individuals), but a statistical chance deviation is equally probable.

In conclusion, the analysis of the family data are in agreement with those of Waldenström (1957) and support the explanation that acute intermittent porphyria, as it occurs in Sweden, depends primarily on a single autosomal gene mutation with phenotypical expression in heterozygotes. The penetrance of this mutation appears complete or nearly complete with respect to a metabolic deviation detectable by an increase of PBG in the urine. Further more or less severe manifestations, elicited by as yet largely unknown factors, may result in the disease known as acute intermittent porphyria. This was the case in about 60 per cent of the presumable heterozygous siblings in this material.

The manifestation of the clinical condition shows association with sex inasmuch as it occurred in 73 per cent (30/41) of female and in 49 per cent (20/41) of male heterozygotic siblings in this material.

Association between acute intermittent porphyria and mental illness

The nature of the association between acute intermittent porphyria and the symptoms of mental illness will be considered in the following analysis. An outline of the problem and the main theoretical alternatives of etiology was given on page 33 and the definition of A- and B-*propositi* on page 35.

The presence and absence of mental illness was determined through personal examination by ordinary psychiatric interview techniques (cf. page 19) and critical evaluation of the files of individuals admitted to psychiatric hospitals. The number of sickness benefit days for mental illness from public insurance funds from 1955 to 1964 was also used as a parameter of psychiatric morbidity (cf. page 56).

The distribution of phenotypes among 76 A- and 73 B-siblings, respectively, is shown in Table 13. Mental illness occurred in a total of 42 siblings of whom 32 belonged to A- and 10 to B-sibships, a difference significant at $P < 0.001$. If we divide the A- and B-siblings, respectively, into those displaying the manifest and/or latent form of AIP and those free of such signs, statistical analysis shows that the frequency of mental illness is higher for the A-siblings in both groups ($P < 0.05$).

Additional evidence supporting the concept that there is a higher, and

Table 13. A- and B-siblings. Distribution of mental illness, manifest AIP, latent AIP and their combinations. The deficit of 18 individuals, as compared to Table 9, is because the psychiatric diagnosis required personal examinations for which only 149 were available.

Sib category	Mental illness present + absent −	Sibling identification						Totals
		Manifest AIP		Latent AIP		Free of AIP		
		+	−	+	−	+	−	
A		14	6	7	10	11	28	76
B		7	8	1	14	2	41	73
Totals		21	14	8	24	13	69	149

perhaps more severe, psychiatric morbidity among the A-siblings is that 12/76, of them as compared to only 3/73 B-siblings, had been certified for care in mental hospitals. Moreover, sickness benefit allowances, because of mental illness, were paid to the A-siblings for an average of 4.2 days per year per individual as compared to 0.5 for the B-siblings (cf. page 59, ff.).

It seems unlikely that the difference in psychiatric morbidity between the A- and B-siblings were caused by one particular clinical and genetical AIP entity in the A- and a different one in the B-families. The results of an analysis of the phenotypical manifestations in the two groups of families are not compatible with such an explanation. Moreover, since 11 of the A- and 11 of the B-families were found to belong to the same pedigree, it seems reasonable to assume that at least these families have the same basic genetical entity. The first seven generations of this pedigree were reported by Bylund (1956).

The significantly higher prevalence of mental illness among siblings of the A-families lacking the AIP-gene as compared to the same category of the B-families suggests an admixture of independently transmitted mental disease in the A-families. However, if this were the complete explanation, and as a consequence implying that the A-*propositi* represented a selection of patients carrying combinations of the AIP-gene and different not closely linked mutations, it follows that carriers and non-carriers of the AIP-gene among their siblings have an equal chance of becoming mentally ill. A calculation (cf. Table 14) shows that the prob-

Table 14. Distribution of mental illness of A-siblings having manifest or latent AIP disease and those without such manifestations.

AIP disease (manifest or latent)	Mental illness		Totals
	Present	Absent	
Present	21	16	37
Absent	11	28	39
Totals	32	44	76

ability for such an exclusive explanation is small ($P < 0.02$). This strongly suggests that there is a positive correlation between AIP-gene carriers and mental illness.

Taken together, the results of these analyses are best interpreted as indicating that the A-families are biologically heterogeneous with respect to the trait which was operationally defined as "mental illness". It should nevertheless be possible to obtain some information about the characteristics, if any, of mental illness as a pleiotropic manifestation of the AIP-gene *versus* mental illness of different origin.

Manifestation of independent recombinations of AIP and mental illness are most likely to be found in those A-families in which at least one sibling is mentally ill and at the same time not an AIP-gene carrier.

In consequence the A-siblings were divided into two groups:

(α) sibships in which the *propositus* had one or more siblings with mental illness but without AIP

(β) sibships in which the *propositus* had only siblings with mental illness combined with AIP.

Eleven of the A-siblings were mentally ill, but free of AIP-genes. They all belonged to six families, (*i.e.* (α) A-sibships) (Table 15). The six (α) A-*propositi* were compared with the 14 remaining (β) A-*propositi*. The main differences are shown in Table 16.

Some pertinent data regarding the six above-mentioned (α) A-*propositi* have been summarized in the following short case reports. The figures after *propositus* indicates the family number, as recorded in the appendix.

Table 15. A-families. Distribution on sibships of siblings mentally ill but without signs of manifest or latent acute intermittent porphyria.

Family number	No. of cases
A (1—7), 9, 10, 12, 14, 15, 18, 20	0
A 8	2
A 11	1
A 13	1
A 16	1
A 17	4
A 19	2
Total	11

Propositus A 8

Woman, 48. Mother latent porphyria. Father periods of depression. At age 39, the patient had depression, suicidal thoughts, and was admitted to a mental hospital. Electro-convulsive treatment and barbiturates were given without side effects.

Propositus A 11

Woman, 47. Father latent porphyria. Mother died in mental hospital, her diagnosis was senile dementia. The patient was treated in three different psychiatric hospitals for depression with suicidal attempts. At age 29 electro-convulsive treatments and in addition different types of barbiturates. Lobotomy at age 41 also legal abortion and sterilization granted because of mental illness. Neurological symptoms lacking. Son, born in 1941 admitted to mental hospital for depressive psychosis.

Propositus A 13

Man, 46. Single case of confirmed AIP in this family. His mother had increased excretion of faecal porphyrins and was possibly an AIP genetic carrier. Patient had vertigo and paraesthesia, suspicion of disseminated sclerosis. AIP provoked by barbiturates. Periods of depressions and occasionally confusional states, reason for admission to a mental hospital.

Table 16. Subdivision of A-*propositi* into those (α) who had one or more siblings with mental illness but without manifest or latent acute intermittent porphyria and those (β) who had only siblings with mental illness combined with acute intermittent porphyria.

Category of A-*propositi* n = 20	Symptom or sign						
	Hallucinations		Neurological signs		Abnormal EEG		Urine PBG mg per gram creatinine. Mean of group
	Present	Absent	Present	Absent	Present	Absent	
(α) n = 6	2	4	2	4	0	4	15
(β) n = 14	9	5	13	1	4	2	38

Propositus A 16

Man, 48. Father AIP. The patient had periods of depression with obsessive-compulsive symptoms. Paraesthesia and gastro-intestinal symptoms. Disability pension because of mental illness.

Propositus A 17

Man, 37. Mother manifest AIP. The patient was of subnormal intelligence. Periods of depression and anxiety. Unable to work due to his mental state. Neurological signs lacking but intermittent gastro-intestinal disturbances.

Propositus A 19

Man, 45. Father alcoholic. Patient's AIP diagnosed at the age of 27. Alcoholic, delirium tremens, suicidal attempts, spent several long periods in mental hospitals. Barbiturates given. Abdominal symptoms provoked by disulfiram.

Neurological symptoms appear to occur more frequently among the 14 (*β*) A-*propositi* than among the 6 (*α*) A-*propositi,* and their urines contained larger amounts of porphyrines (cf. Table 16). This suggests that the psychiatric symptoms of the 6 (*α*) A-*propositi* to an appreciable extent have an origin independent of the AIP disease.

In the 14 (*β*) A-families the 12 siblings who were AIP-gene carriers and mentally ill probably constitute a biologically more homogeneous group, in which the altered metabolism of AIP could be the main cause of the mental symptoms. Of these 12 siblings 9 had AIP in clinically manifest form. Only one of these nine individuals displayed symptoms of a schizophrenic psychosis and is described and discussed as follows.

Case 6 B: 1. Woman, 42. Her father had clinical symptoms of AIP and died in a mental hospital. At 17 the patient began telling people that she was a movie star. Occasionally she became excited but the exaltation could rapidly change into depression. She also heard voices telling her to take her own or somebody elses life and she showed violent outbreaks against others. When admitted to a mental hospital at the age of 18 she displayed stereotypies, disconnections, incoherence, visual and auditory hallucinations and aggressiveness, symptoms which proved to be resistent to various forms of pharmacological treatment. She was lobotomized 14 years after admission. After the operation she became quiet and cooperative but lost initiative and was unable to care for herself and for this reason remained in the hospital. At the age of 28 she had acute attacks of abdominal pain and dark urine and a diagnosis of AIP was confirmed. She did not have any neurological signs or symptoms and her gastro-intestinal disturbances were of short duration when compared to the long period with psychotic symptoms.

It is not possible, at present, to determine if the symptoms of schizophrenia and the abdominal symptoms are of similar origin and caused by the AIP disease. Schizophrenia or schizophrenia-like psychosis have been reported associated with AIP (Waldenström 1937, Freeman and Kolb 1951, Delay *et al.* 1961, Peters 1962). Of the 149 full siblings personally examined in this study, only two were diagnosed as having schizophrenia. The second case (**17**: 5) belonged to the 11 (α) A-siblings with mental illness but free of AIP, and is described in this context since it was the only case in this group who presented symptoms of a major psychosis.

Case **17**: 5. Man, 35, unmarried. In school he was shy and withdrawn and later had socializing problems. Gradual development of bizarre hypochondrical ideas, passivity, periods of psychotic states with auditory hallucinations. He was unable to work and was exempt from military service. Hospitalized at age of 24 after a period of psychomotor unrest, anxiety, catastrophy feeling, religious speculations, lack of concentration and paranoid ideas. After the introduction of chlorpromazine he received large doses with favorable results. The findings of the psychological examination, at the age of 33, were interpreted as supporting the clinical impression that the mental impairment was due to residue of a previous active schizophrenic process.

Since the special case of 6: B1 (one among 9 siblings of the 14 (β) A-families) has been discussed above, the remaining 8 siblings were compared with the 7 B-siblings with manifest AIP and mental disease (cf. Table 17). These fifteen individuals, who were largely similar with

Table 17. Comparison of selected A- and B-siblings (as explained in the text) with manifest AIP and mental illness.

Family category	Symptom or sign					
	Confusion		Hallucinations		Neurological signs	
	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent
A siblings n = 8	2	25	2	25	2	25
B siblings n = 7	5	71	3	43	5	71
Totals	7	47	5	33	7	47

respect to mental symptoms and neurological signs, should represent a fair approximation of a patient group with manifest acute intermittent porphyria and mental illness of common origin. Such a mental illness of basically the same molecular origin as AIP will be called an AIP mental syndrome.

This group of 15 patients was compared with the 11 (α) A-siblings who were mentally ill but free of the AIP-gene and with 10 siblings from the 14 (β) A- and of the B-families who had manifest AIP but were free of mental illness (cf. Table 18).

As a consequence of the analyses and the considerations explained in this chapter the three groups of patients in Table 18 have been selected so that they are likely to represent the following three etiological categories: (1) manifest AIP with AIP mental syndrome, (2) manifest AIP without mental illness and (3) mental illness etiologically independent of AIP.

Groups (1) and (3) differ mainly with respect to hallucinations, confusion and neurological signs which occur predominantly among the patients of group (1). All 11 patients of group (3) and all except one (case **31**: 2) of the fifteen patients of group (1) had experienced periods of mental depression. In group (1) neurological signs and symptoms had been noted for 7 patients, all of whom had also shown confusional states and 5 of them had, in addition, experienced visual hallucinations. The remaining 8 patients had no record of confusion, hallucinations or neurological signs.

Table 18. Distribution of symptoms (as defined on page 19) of patients selected tentatively as representing cases of manifest AIP and mental illness probably of common origin, *i.e.* group (1), cases with manifest AIP without mental illness, group (2), and cases of mental illness not associated with AIP, group (3).

Observation	Symptoms present in					
	Group (1) Probable AIP mental syndrome n = 15		Group (2) Manifest AIP without mental illness n = 10		Group (3) Mental illness without AIP n = 11	
	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent
Anxiety	15	100	1	10	11	100
Insomnia	15	100	4	40	11	100
Depression	14	93	0	0	11	100
Certain types of emotional disturbances	10	67	1	10	5	45
Confusion	7	47	1[1]	10	2[2]	18
Neurological signs	7	47	4	40	0	0
Hallucinations	5	33	0	0	1	9
Attempted suicide	3	20	0	0	4	36

[1] Following subarachnoid hemorrhage.

[2] One case following alcohol intoxication.

The patients of group (3) had no record of neurological signs, confusional or hallucinatory states but for two exceptions (cases **17**: 5 with a diagnosis of schizophrenia and **16**: 11 described below) (cf. page 48).

Case **16**: 11. Female, 44. Lost two of her three children, one boy died when one year old, probably of acute intracerebral hemorrhage and another boy was killed in an automobile accident at the age of 6. She was divorced at 35, and after this she had difficulties in her work and started to drink. During the past ten years she had periods of depression for which she was treated in a mental hospital. On one occasion she had a confusional state of brief duration following heavy drinking and menorrhagia with major loss of blood.

Mental depressions were defined, for the purpose of this investigation, basically in terms of effect on daily routine activities and working/earning capacity. The histories, in particular concerning periodicity and duration, the mental symptoms, psychological data, the degree of working incapa-

city associated with the depressive illnesses indicate a striking similarity between the depressive syndrome of the 11 group (3) patients, including the patient with schizophrenia, and the 8 patients of group (1) who had not displayed any neurological signs.

On the basis of their clinical features and histories all 19 patients could be diagnosed as depressions. No decision can be reached, at present, as to the etiology of the depressions of the 8 patients of group (1) who have just been discussed, since some of them may have depressions of origin different from the symptoms causing AIP and thus not represent an AIP mental syndrome. Thus, although of superficially similar clinical symptomatology, the syndromes may include several etiological entities, genetical as well as environmental.

The depressive aspect of the syndromes present in 6 of the 7 patients in group (1) who had neurological signs, confusional states and frequently visual hallucinations did not appear to differ in character from that of the 11 group (3) patients.

The method of ascertainment makes it likely that the 7 group (1) patients would exemplify, most closely, the actual AIP mental syndrome.

Even though there should be a slight difference in degree of severity of depression between the postulated AIP mental syndrome, and other depressions in this material, it is of small differential diagnostic value. Nevertheless because of certain observations, it can be tentatively concluded that the mental illness which develops in patients with AIP disease is likely to have identical etiology (AIP mental syndrome) if there is the following combination of signs or symptoms: (a) slight to moderate depression; (b) transitional confusional states; (c) frequent visual hallucinations; and (d) neurological signs. This does not imply that an AIP mental syndrome requires also the presence of abdominal and neurological symptoms for its manifestation. As further evidence is lacking this question must await future clarification. Moreover, the mental manifestations of the AIP-gene should be expected to show considerable individual variability, perhaps from slight mental depressions to major psychotic states. Such a latitude would correspond with the latitude of the clinical somatic manifestations of the AIP-gene as observed in different individuals (Waldenström 1937, 1957).

The psychiatric symptoms which were interpreted as alternative manifestations of the genetically determined deficiencies of porphyrin metabolism underlying the somatic manifestations of AIP, are further ex-

emplified by the histories and observations of the 7 patients of group (1) who had neurological signs. The depressive syndrome present in six of the seven cases, (except **31**: 2) as indicated in the appendix, was not specific of type and not recorded in the following case histories.

Case **9**: 1. Man, 57. Father had manifest AIP. At 25 the patient had his first attack with abdominal pain and dark urine. He was given barbiturates several times and had considerable gastro-intestinal disturbances. He found that alcohol relieved the pain for short time, then the symptoms were aggravated. At 48 he experienced an attack with confusion and visual hallucinations in which he saw his wife and some friends visiting him at night in the hospital. At one time the confusional state developed during cortisone treatment. He also had severe pain in arms and legs and developed paralysis from which he did not recover; even 9 years later he showed at examination residual partial bilateral weakness with claw-hands and foot-drop, but no sensory loss. At 55 a co-existing arthritis urica was diagnosed.

Case **12**: 5. Man, 43 years old. Mother AIP and periods of depression. At 35 the patient had his first attack of AIP with abdominal symptoms and dark urine and the following seven years several periods, 7—14 days in duration, of abdominal pain, weakness and paraesthesia in his arms. On one occasion he saw birds flying through the room with his clothes in their bills, and he was anxious when he saw that the window had turned 90°. At the age of 39 he had gynecomastia for about six months, and during the past two years has had periods of impotence. He is the father of four children.

Case **25**: 5. Man, 53. His paternal aunt died from AIP. He had at least 30 acute attacks in the past 20 years, characterized mainly by abdominal and muscular pain. Occasionally he used large quantities of alcohol. Distal paralysis developed in the arms, at 47. In the last years he has been concerned with metaphysical speculations, and during attacks had visual hallucinations and disorientation. He died in 1965 during an acute attack mainly due to cardio-vascular insufficiency. The AIP disease in this patient may have been enhanced by chronic lead intoxication from eating fish with high lead content.

Case **27**: 4. Woman, 57. Twin sister died from respiratory insufficiency in an acute attack of AIP. Tuberculosis 1925. For many years she had constipation and abdominal cramps but not until 35 was the abdominal pain severe enough to warrant laparatomy. She also suffered from insomnia and was sometimes awake all night in spite of large doses of barbiturates. The weight went down from 60 to 42 kg in a few weeks. The left knee and the ankle jerks could not be evoked. Sensory impairment in distal legs was recorded. After the operation she developed depression, severe anxiety, saw men at night in her room, heard somebody calling for her, and heard songs and talked to voices

but did not at any time show a paranoic state. After the attack she was very weak and did not recover; 22 years after the attack she still had a residual bilateral partial weakness of dorsi-flexion of the feet and partial bilateral claw hands. She had no later attacks with neurological impairment, but many 3—4 day periods, when she was between 35 and 40, of abdominal pain and insomnia. In the last decade no symptoms of AIP except for the residual partial weakness of feet and hands.

Case 28: 4. Woman, 65. No children and menopause at 33. She had noticed dark urine, and suffered from attacks of abdominal pain and severe constipation which needed laxatives for many years. The AIP disease was diagnosed at the age of 40. At 58 when taking medication containing barbiturates for insomnia and hypertension she experienced diplopia, memory disturbances, severe anxiety, confusional state with perplexity and bewilderment, and paralysis that came and went suddenly. Such periods of paralysis, during which the patient could not move, were present even on occasions when no barbiturates were received. Even between the attacks she was very weak and reported that she dropped things if the weight was more than 3—4 kg.

Case 31: 2. Woman, 31. She had her first, and so far single, attack of AIP at the age of 15. The attack of acute abdominal pain started on the third day of an acute sore throat infection with a temperature as high as 39° C. On the fifth day she was given Saridon® (1-phenyl-2,3-dimethyl-4-isopropyl-5-pyrazolon, acethyl-p-phenetidin, 3,3-diethyl-2,4-dioxo-tetrahydropyridin and 1,3,7-trimethyl-2,6-dioxopurin) for symptomatic relief but the *post hoc* reaction was dramatic. She first had cramps of her right arm and leg which were followed by generalized convulsive seizures, loss of consciousness and urinary incontinence. On admission to the hospital she was in a state of great anxiety and refused to cooperate. Her condition improved gradually and after a period of two weeks she had made a complete symptomatic recovery. She had since led a normal life and continued to be free of the earlier experienced or other symptoms of AIP.

Case 36: 4. Woman, 21. Father's sister died in an acute attack of AIP. The patient had attacks of severe abdominal pain at the age of 14. At 17, two months after a slight accident, she displayed cramps in her right arm and leg and visual hallucinations. EEG was at that time abnormal. Although she was given large doses of barbiturates she improved and EEG became normal. At 20, abdominal pain, dark urine and the diagnosis AIP was verified. She has since had repeated attacks of abdominal pain, severe anxiety, on one occasion following administration of oral contraceptives.

It is likely that some of the mental symptoms, which occur during attacks of AIP, are caused by metabolic changes (cf. Gray 1966), apparently

often temporary and reversible, which affect the nervous system (Dow 1961, Rey-Bellet 1964). However, in some cases such changes are not completely reversible, and lesions of the peripheral nerves (*e.g.* Heirons 1957) as well as in the brain (Perlroth *et al.* 1966) have been found. Occasionally permanently disturbed function of the peripheral nerves or defects of memory, judgment, comprehension or emotion occur as evidence of remaining focal lesions in the central or peripheral nervous system (Melkersson 1926, Waldenström 1937, Goldberg 1956). It is, of course, possible that such permanent lesions occur during every severe attack of AIP provided most of them remained localized in "silent" areas of the nervous system or in areas where loss of function could be easily compensated. This explanation, which does not have to include an hypothesis of a special vulnerability of certain individuals to the metabolic error of AIP after it has been established as a clinical condition, is compatible with the frequency in which mental disease appears to be a direct consequence of the same molecular pathology which causes the manifestation of the AIP disease. Considering that 23 of the 95 *propositi* with verified manifest AIP were identified as mentally ill and that 14 of the 20 patients classified as A-*propositi* were finally considered as having AIP disease and mental illness of common origin, the frequency of AIP-associated mental illness can be estimated as roughly 17 per cent. Another estimate, still more uncertain because of small numbers, can be based on the fact that 7 out of 16 B-siblings probably belong to the same etiological group, *i.e.* roughly 40 per cent. As it is highly likely in an investigation of this type that selection of the *propositi* is biased by the more rigid application of the diagnostic criteria than used for identification of the secondary cases, the two estimates, at best, would give only the lower and upper limits. So, with reservations for all insecurities inherent in this material, the estimated risk that attacks of AIP cause, simultaneously, central nervous system lesions extensive enough and/or so located as to cause mental illness, would occur with a frequency ranging from 1/6 to 1/3 of the patients. Waldenström (1937) found that around 20 per cent of 103 AIP patients displayed pronounced mental symptoms. In a larger sample of 233 cases of AIP 28 per cent had a history of delirium, 16 per cent hysteria and 11 per cent apathy (Waldenström 1957). These figures largely agree with the findings in the present material. As mentioned above, the explanation does not exclude the fact that lesions could be present in the remaining 5/6 to 2/3 of the patients, but by

chance are restricted to "silent" areas, subjected to compensation or of very small size. As a working hypothesis it has, at least, the merit of being accessible to suitable tests by properly arranged animal experiments and, perhaps, histological or histochemical *post mortem* investigations of patients.

The interpretations which have been presented are, at best, probably reasonably correct simplifications of a complexity of pathological processes mutually affecting each other, influenced by a multitude of independent special factors and subject to modification by genetical and environmental factors which determine the personality of the individual and as a consequence modify his mental symptomatology following organic damage.

Attempts have been made to explain the psychiatric symptoms in AIP partially as a reaction to a prolonged misdiagnosed or undiagnosed illness, and the following lack of understanding on the part of the physician (Waldenström 1937, Whittacker and Whitehead 1956). Others have pointed out that such factors as stress caused by the sudden death of a close relative during an AIP attack, dependency on others because of physical incapacity, fear of family disruption etc., may become superimposed on symptoms of direct molecular origin and lead to a variety of grossly psycho-pathological syndromes (Eldahl 1938, Roth 1945, Schneck 1946, Eilenberg and Scobie 1960). However, if such psychogenic factors are decisive for the development of mental disease in the AIP patients, they should also affect all of their family members with AIP regardless of the occurrence of mental illness in the *propositus*. As this is contrary to the observations in this investigation, it has to be concluded that the importance of psychogenic mechanisms is restricted to modifications of processes basically controlled by biochemical misfunctions.

The higher risk of developing a mental disease for the siblings of the A-*propositi* than of the B-*propositi* is best explained as the result of inclusion of some A-*propositi* who were affected with independently segregating genetical mental syndromes predominantly of depressive types.

Although the AIP mental syndrome is nothing but a description of the most frequent symptoms of an organic brain syndrome, with adequate information about the parents and siblings of an AIP patient who presents a mental syndrome, and an evaluation of his symptomatology as outlined, it should be possible to reach a decision between the likelihood

of the presence of an AIP mental syndrome or, alternatively, an independent mental syndrome of genetical or environmental origin. As the latter combination may exist in many porphyric patients with mental disease, it is clear that a proper differential diagnostic evaluation may be of great importance in the choice of adequate treatment.

Waldenström (1939) had the impression that psychosis of manic-depressive type or schizophrenia were relatively common in families with AIP. No case with a manic psychosis and only two patients with schizophrenia were diagnosed among 157 siblings, *i.e.* 1.3 per cent in the present material. This figure is no higher than the figures of the morbidity risk of 1.6 per cent for schizophrenia in a West Swedish population (Larsson and Sjögren 1954) or the cumulative risk of 1.5 per cent in a South Swedish population up to the age group 60—69 years (Hagnell 1966). In an isolated population in North Sweden the calculated probability of becoming schizophrenic was found to be around 3 per cent (Böök 1953). Only one case of mental retardation was found among the 157 siblings and in a man free of AIP.

Since the applied operational definition of mental illness is somewhat different from that used by other workers, the figures of psychiatric morbidity obtained in this investigation can not be strictly compared with the other series. The rate of consulting a psychiatrist or frequency of admittance to a psychiatric hospital for the siblings are not comparable with most other samples examined in Sweden since the number of psychiatrists in North Sweden is low and the distance and communication facilities for reaching a psychiatric hospital are different. The best, available material for comparison of psychiatric morbidity in a Swedish population sample is the estimated cumulative risk of contracting a mental illness of severe impairment up to 60 years of age, which is 7.9 per cent for men and 15.4 per cent for women (Hagnell 1966).

If we consider that the present data, from the family material, do not suggest significant associations between AIP and the schizophrenic and manic-depressive syndromes or mental retardation, the observed incidence, as defined, of some 20 per cent of the AIP *propositi* having mental illness appears high, and rather supports the conclusion that an AIP mental syndrome is likely to be a reality.

V. MEDICO-SOCIAL OBSERVATIONS

This section describes the benefits received by the *propositi* and their siblings from the public insurance funds from 1955 through 1964. It also includes some observations of the marriage frequency and occupational status for an appreciation of the social adjustment.

National Health Insurance and acute intermittent porphyria

Insurance by membership in public insurance funds has been compulsory from January 1, 1955 for practically all permanent residents in Sweden 16 years of age and older. Copies of the disability records were obtained for all members of the 40 family sample who had been insured during this ten-year period. The records contain information relating to periods of sickness and corresponding diagnoses, and possible disability pension.

The maximum length of time during which daily allowances and/or free hospitalization could be granted for the same disease was 730 days (since 1963 no such restriction). If, after this period of time, the patient was still unable to work because of the same disease, and was considered likely to remain in this condition for a considerable length of time, he would receive a disability pension. Disability pensions are registered with the National Social Insurance Board, and information was secured from this source. For the few patients who were not eligible for daily allowances, their periods of sickness were equated to periods of hospitalization.

For the calculation of average annual number of sickness benefit days in different groups only the total number of years within the ten-year period during which insurance was effective, were calculated, exclusive of periods with disability pension.

Diagnoses relating to the different sickness periods were divided into four main groups, *i.e.* acute intermittent porphyria, mental diseases, accidental injuries and other conditions. One diagnosis, only, was regis-

Table 19. Sickness benefit days per member and insurance year from 1.1 1955 to 31.12 1964, and disability pension years for the 40 *propositi*. Less than 2 per cent were half day benefits which were counted as full days. *Propositi* A and B as defined in the text, page 35.

Diagnosis	*Propositi A*			*Propositi B*		
	Male n = 8	Female n = 12	Total n = 20	Male n = 9	Female n = 11	Total n = 20
Porphyria	17.3	26.5	22.8	7.5	4.5	5.7
Psychiatric	20.7	26.5	24.2	0.1	0.1	0.1
Injury	14.8	0.4	6.3	3.7	0.6	1.9
Other	17.7	20.7	19.5	18.9	11.3	14.6
Total	70.5	74.1	72.7	30.2	16.4	22.3
Years at risk	69	102	171	80	104	184
Disability pension, years	11	17	28	10	—	10

tered for each period of sickness. When two or more diagnoses had been recorded for the same period, one was chosen with the following order of priority: 1) psychiatric, 2) porphyria, 3) injury and 4) other.

The A-*propositi*, when compared with the B-*propositi*, had received more sickness benefits in terms of daily allowances as well as disability pensions (cf. Table 19). The high figure for injury among the A male *propositi* is due to a single individual (14: 2) who received sickness benefits for 830 days because of injuries sustained in an automobile accident. Even though no statistical verification was carried out the figures suggest that the A-*propositi* had received considerably more daily sickness benefits than had their B counterparts under the diagnosis of porphyria, *i.e.* 23 days as compared to 5.7, as well as under psychiatric diagnoses, *i.e.* 24.2 days for the A- and 0.1 for the B-*propositi*. Total figures for the A- and B-siblings (cf. Table 20) were 26.4 and 15.7, respectively. Finally, the A-siblings had accumulated more disability pension years, *i.e.* 37 as compared to 20 for the B-siblings.

There were no significant differences with respect to sex within or between the two different sibling groups. As measured by sickness benefit days per individual and year the A-siblings showed a higher psychiatric morbidity as compared to the B-siblings, *i.e.* 4.2 days and 0.5, respectively.

Table 20. Sickness benefit days per member and insurance year from 1.1 1955 to 31.12 1964, and disability pension years for 156 siblings of the 40 family sample. Siblings A and B as defined in the text, page 35.

Diagnosis	Siblings A			Siblings B		
	Male n = 41	Female n = 38	Total n = 79	Male n = 46	Female n = 31	Total n = 77
Porphyria	3.5	0.9	2.3	0.2	0.7	0.4
Psychiatric	3.7	4.7	4.2	0.1	0.9	0.5
Injury	2.5	0.2	1.4	2.2	0.9	1.6
Other	17.4	19.8	18.5	12.8	13.8	13.2
Total	27.1	25.6	26.4	15.3	16.3	15.7
Years at risk	387	322	709	399	282	681
Disability pension, years	13	24	37	10	10	20

The six (α) A-families (cf. page 45 and Table 15) in which one or more siblings were mentally ill but free of the AIP-gene also averaged a slightly higher psychiatric morbidity than the rest of group A-families. When acute intermittent porphyria alone is considered, and all the 40 families are taken into account, it emerges that the ratio of overall registered morbidity for the group with manifest form of AIP, to those with the latent form and those lacking manifestation of either type is 42: 20: 17 days per sibling and insurance year.

When compared in terms of the four main diagnostic groups, the A-siblings with latent AIP or free of AIP showed a higher morbidity than the same categories of B-siblings.

For the total material the ratio of morbidity did not appear dependent on age. When divided into age groups of 16 to 44 years and 45 to 66 years, the figures are 22 days for the younger and 20 days for the older age group. The disability pension figures of 9 years for the younger and 41 for the older group is, of course, not surprising. The ratio of morbidity of all A- and B-siblings who carried the psychiatric diagnoses, as compared to their siblings without such diagnoses was 42 days *versus* 13 days. The disability pension figures were 28 and 29 years, respectively.

None of the siblings had become eligible for a disability pension only for the reason of being a victim of AIP. In fact, mental illness was the

Table 21. Sickness benefit days per individual and insurance year during 1955—1964 among 156 siblings of the 40 family sample, compared with the general population in Sweden 1963—1964, (Riksförsäkringsverket 1965, 1966).

Age groups in years	No. of days for 156 siblings of the AIP families	No. of days in the general population
16—44	22.0	10.0
45—66	20.2	19.5

decisive reason for certification and accounted for 28 disability pension years, with rheumatoid arthritis, cardio-vascular diseases and parkinsonism following encephalitis letargica for the remaining 29 years.

The average number of sickness benefits days for all eligible and registered Swedish residents in terms of age groups was available from annual reports of the National Social Insurance Board (Riksförsäkringsverket 1965, 1966) for the two-year period 1963—1964 and are shown in Table 21. Corresponding averages for the whole ten-year period 1955—1964 were calculated for all siblings of the A- and B-families with exclusion of the *propositi*. As the numbers were relatively small they were divided into only two age groups. The siblings have a higher average morbidity than the general population insured by the public insurance funds. However this is conspicuous only in the lower age group, *i.e.* below 45 years.

Marriage frequency

The marriage frequency among all A- and B-siblings, including the *propositi*, with the manifest form of AIP for three age groups between 20 and 69 years, is shown in Table 22. In a total of 72 individuals, 51 were married and had living partners in 1964 as compared to the expected 53 if based on the marriage frequency in corresponding age and sex groups of the entire population for 1964 (Statistiska Centralbyrån 1965). Thus it follows that the patients with manifest AIP do not appear to differ from the total population in respect of marriage frequency.

If these figures are taken as a measure of the degree of social adjustment as well as of the chance of reproduction the AIP patients do not

Table 22. Marriage frequency for different age groups of 72 siblings with clinical manifest form of acute intermittent porphyria compared with the general population in Sweden 1964.

Age (years)	Total number of siblings	Observed no. of married siblings	Expected no. married (relative to the general population, 1964)
20—29	8	4	4
30—49	37	27	30
50—69	27	20	19
All	72	51	53

differ from the total Swedish population, but do differ from patients with some other hereditary diseases causing disablement, *e.g.* osteogenesis imperfecta (Berfenstam and Smårs 1961).

No marked differences between the sexes were found in this material in respect to marriage frequency, and therefore figures for the sexes are not tabulated separately.

Occupation

The occupation of the siblings varied, but most were doing manual work. Working capacity was severely affected in four patients, three of whom had AIP (Table 23).

In some cases the choice of occupation may have been influenced by the disease. Patient **16**: 10 started in his twenties as type-setter but was unable to complete his training because of frequent attacks of severe abdominal pain. It is possible that his attacks were caused by lead exposure, a well known hazard of this profession. The patient changed his occupation and is now making his living as an artist. Another patient **19**: 8, a plater, suffered severe attacks of abdominal pain when welding sheet-metals painted with red-lead. Patient **25**: 5 experienced acute abdominal symptoms after eating certain lake fish later shown to contain an unusually high lead content (cf. Wetterberg 1966). These observations suggest that patients with AIP run a risk of acute attacks following lead exposure.

Patient **20**: 1 held a well paid position in a factory, but had to remain

Table 23. Distribution of the 196 siblings of proband generation in the different occupational groups.

Occupation	Males			Females			Total		
	With AIP	Without AIP	Total	With AIP	Without AIP	Total	With AIP	Without AIP	Total
	n = 52	n = 52	n = 104	n = 56	n = 36	n = 92	n = 108	n = 88	n = 196
Public service employees	2	4	6	15	11	26	17	15	32
Workers in trade and commerce	5	10	15	7	7	14	12	17	29
Agricultural, forestry and fishery labourers	12	13	25	4	2	6	16	15	31
Road workers and carpenters	6	4	10	—	—	—	6	4	10
Industrial workers and craftsmen	16	13	29	1	1	1	17	13	30
Transport workers	7	4	11	—	—	—	7	4	11
Artists	1	—	1	—	—	—	1	—	1
Students	—	1	1	1	1	2	1	2	3
Teachers	—	2	2	2	1	3	2	3	5
Housewives	—	—	—	23	12	35	23	12	35
Old age pensioners	3	1	4	—	1	1	3	2	5
Disability pensioners	—	—	—	3	1	4	3	1	4

at home one or two days every week because of abdominal pain. This finally forced him to resign and take up work which did not require regular hours.

Although, the disease had affected the choice of occupation for some individuals, as a group the AIP patients did not differ significantly from their non-affected siblings. This is probably because the choice of occupation is usually made before the age of onset of the disease.

VI. EPIDEMIOLOGICAL ASPECTS

In 1964 there was a total of 461 living individuals with manifest acute intermittent porphyria in Sweden, corresponding to 1/13,000 individuals 15 years of age and older. The disease, however, is not randomly distributed.

Of the A- and B-siblings, 73 per cent (144/196) were born in the two northernmost counties, *i.e.* Norrbotten and Västerbotten (region I in Fig. 3) which include only 6.4 per cent of the total population.

At the end of 1964, 56 per cent of these siblings were still residing in the same region. Migration of those who had moved from the area was consistent with the general pattern of migration for this part of Sweden (Helmfrid 1963, Törnqvist 1963, Tryggveson 1967).

Applying the same percentage (56) to the total of 461 porphyrics, the prevalence in the population 15 years of age and older of region I was estimated at 1/1500.

The frequency of AIP-genes can be estimated as follows. The penetrance of manifest AIP calculated from the A- and B-sibships is 0.66 (29/44, cf. Table 12). Thus, assuming that 56 per cent (258/461) of the heterozygotes (*i.e.* manifest plus latent cases) 15 years of age and older were also residing in region I at the end of 1964, the frequency of heterozygotes in this area would be approximately 1/900 individuals and the gene frequency 1/1800. For the remaining Swedish population (5.7 millions in the same age group) the corresponding frequency of heterozygotes will be 1/20,000, and the gene frequency 1/40,000.

It is apparent from Fig. 3 that the frequency decreases from the north to the south of the country. Available migration data indicate that the AIP-gene is disseminating south into the population from region I.

In Fig. 3 Sweden is shown divided into four parts. Regions I and II are considerably less industrialized and urbanized and less densely populated than regions III and IV. The extent of migration is similar for the

Fig. 3. Regional distributions by place of birth and residency in 1964, for 196 of the A- and B-siblings (cf. page 35) and the 95 patients with acute intermittent porphyria representing a random sample of all Swedish cases. Population: region I

sample of 95 porphyrics, and the porphyrics and the siblings free of the AIP disease belonging to the A- and B-families as reflected by place of birth and place of residency in 1964. Moreover, they are consistent with the general migration pattern for regions I and II, *i.e.* a major flow into region III and a smaller one into region IV.

This pattern of dissemination as well as the relatively large number of heterozygotes who experience only slight clinical manifestations or none at all suggest that the selection against the mutation cannot be a strong one. The epidemiological behaviour of this mutation, therefore compares well with what is known about the origin and spreading of the so called South African form of porphyria, in which one ancestor born in the Netherlands and emigrating to South Africa where he married at the Cape in 1688, is supposed to have transmitted the disease to thousands of South Africans (cf. Dean 1963).

373,736, region II 774,407, region III 3,342,603 and region IV 1,565,798 individuals 15 years of age and older.

The degree of industrialization is lowest in region I, region II differs slightly while the highest degree of industrial development is in region III and IV (Helmfrid 1963, Törnqvist 1963, Tryggveson 1967).

◘ = sample of 95 AIP *propositi*, ● = A- and B-siblings, manifest and latent cases, ○ = A- and B-siblings, normal.

B = place of birth

R = place of residence

SUMMARY

1. The main purpose of this investigation was to study the type and nature of psychopathological manifestations associated with acute intermittent porphyria (AIP) in Sweden. In addition, the frequency of AIP in mental hospital populations and some clinical, genetical, epidemiological and social aspects of the disease have been investigated.

2. Individuals with increased urinary excretion of porphobilinogen (PBG), but without signs or symptoms of clinical disease were classified as *latent* cases of AIP. Patients who, in addition to their positive biochemical tests, had displayed abdominal and/or neurological signs or symptoms characteristic of acute porphyria were classified as cases with *manifest* AIP.

Individuals showing at least three of the following seven signs or symptoms were operationally classified as patients with *mental illness*: confusion, hallucinations or illusions, depression, suicidal thoughts or attempts, anxiety, certain other types of emotional disturbances (apathy, ambivalence, depersonalization, immaturity) and insomnia.

3. In a random sample of 1907 patients of two mental hospitals in northern Sweden manifest AIP was identified in three cases, *i.e.* roughly in one of 600.

4. The urines of 170 of the above patients (9 per cent) showed an above normal extinction when measured for PBG according to the method of Mauzerall and Granick (1956). It was possible to reexamine the urines of 73 of the patients including the three AIP patients. In these three AIP cases the urinary compound reacting with Ehrlich reagent showed the typical extinction curve for PBG with maxima at 525 and 555 nm. In the remaining 7 cases the reacting compound was shown to differ from PBG by a flat extinction curve with a plateau around 560 mm, and UV fluorescence.

Of the 170 patients, with an increased quantity of the urinary com-

pound, 75 per cent were on more than 200 mg phenothiazines daily as compared to 3.5 per cent in a control group of 200 patients from the same hospitals.

5. An analysis was made of the distribution of AIP and psychiatric illness among parents and siblings of a 40 family sample, obtained through randomly selected *propositi* from the 461 registered cases of manifest AIP in Sweden at the end of 1964. The 40 family sample consisted of the parents and siblings of a sample of 20 *propositi* displaying AIP as well as mental illness (A-families, sibships) and another sample of 20 *propositi* with AIP but without evidence of mental illness (B-families, sibships). A personal field investigation was carried out, and of the 227 living members of the 40 family sample, 225 were examined using ordinary psychiatric interview techniques.

6. The genetical analysis supports the view that acute intermittent porphyria, as it occurs in Sweden, depends primarily on a single autosomal dominant gene mutation with phenotypical manifestation in heterozygotes. The error in porphyrin metabolism can be identified in practically all heterozygotes by measuring urinary porphobilinogen in individuals above 15 years of age. The manifestation of the clinical condition occurred in 73 per cent (30/41) of the female, but only in 49 per cent (20/41) of the male heterozygotic siblings.

7. The data do not support the contention that maternal age, abnormal pregnancies or birth rank is of importance for the occurrence of AIP.

8. The 20 A- and the 20 B-sibships were compared with respect to psychiatric morbidity. Of 42 siblings with mental illness, 32 were A- and 10 were B-siblings. Moreover, the significantly higher prevalence of mental illness among A-siblings who were free of the AIP-gene, as compared to the same category of B-siblings suggests an admixture of independently transmitted mental disease of genetical etiology. There was, however, also a positive correlation between AIP-gene carriers (*i.e.* all heterozygotes) and mental illness.

9. Three groups of patients likely to represent three etiological categories were selected:

(1) 15 patients (selected from 32 sibships) with manifest AIP and mental illness, whose mentally ill siblings all had manifest or latent AIP.

(2) 10 patients who had manifest AIP but were free of mental illness.
(3) 11 patients from 6 A-families with mental illness independent of AIP.

Groups (1) and (3) differed mainly with respect to the frequency of confusion and visual hallucination and neurological signs which occurred predominantly among the patients of group (1). Depression was the most frequent diagnosis in group (3), *i.e.* in all the 11 patients. A further analysis of the 15 cases of group (1) revealed that seven patients had developed a polysymptomatic mental illness which may represent a genuine AIP syndrome while eight patients had only depressions similar to group (3). The tentative conclusion is that there may be a genuine AIP mental syndrome which should be suspected when the following signs or symptoms are present: (a) slight to moderate depression; (b) transitional confusional states; (c) frequent visual hallucinations; and (d) neurological signs.

10. The severety of sickness or incapacity as measured by the number of days with sickness benefit allowance paid per individual during a ten year period showed higher figures for individuals with latent AIP than for their siblings who were free of the AIP-gene and still higher for patients with manifest AIP. The number of sickness benefit days was also higher for siblings with mental illness than for siblings without mental illness irrespective of whether or not they had any form of AIP. The younger age groups were comparatively more incapacitated by illness than the average insured person, as indicated by the increased morbidity between the age of 16—44 years.

11. The prevalence of manifest acute intermittent porphyria in the total Swedish population 15 years of age and older in 1964 was calculated at 1/13,000. However, there was a strong concentration in the two most northern counties (prevalence 1/1500 individuals). The disease may be disseminated by migration of carriers south to the more industrialized and urbanized areas of the country. These migrations were consistent with the general population movements in Sweden.

For the two northern counties (population 15 years of age and older 373,736) the AIP-gene frequency and the frequency of all heterozygotes were estimated to be 1/1800 and 1/900, respectively, while for the rest of Sweden (population 5,682,808) the corresponding figures were 1/40,000 and 1/20,000.

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APPENDIX

P	propositus
Fa	father
Mo	mother
M	male
F	female
m	manifest form of acute intermittent porphyria
l	latent form of acute intermittent porphyria
0	unaffected of acute intermittent porphyria
ALA	δ-aminolaevulic acid
PBG	porphobilinogen
+	present
–	absent
	no information
†	deceased

The siblings who were deceased before 15 years of age are not included in the appendix.

The following six cases reviewed by Waldenström (1937) are included in the present appendix:

Case number in the appendix	Case number in the monograph of Waldenström
16: 5	28
16: 6	29
16: 9	30
16: 10	31
20: Mo	103
21: A: 1	61

Family number	Family identification	Sex	Age 31.12 1964 or at death	Age of onset of manifest AIP	AIP m, l or 0	Psychiatric hospital admission	Confusion	Hallucinations or illusions	Depression	Suicidal thoughts or attempts	Anxiety	Certain types of emotional disturbances	Insomnia	Neurological symptoms	Abdominal symptoms	Barbiturates	ALA mg/g creatinine	PBG mg/g creatinine
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	Mo	F	58	29	m	–	+	+	+	–	+	–	+	+	+	+	6.3	9.3
	1	F	26†	23	m	–									+			
	2	M	29		0	–	–	–	–	–	–	–	–	+	+	+	0.9	1.9
	P 3	F	26	16	m	+	+	+	+	+	+	+	+	+	+	+	88	140
	4	F	17		0	–	–	–	–	–	+	–	+	–	–	–	2.9	2.9
2A	Fa	M	51		0	–											3.1	1.1
	Mo	F	56	38	m	–	+	+	+	+	+	+	+	+	+	+	4.8	8.4
	P 1	F	28	20	m	+	+	+	+	–	+	+	+	+	+	+	43	140
2B	Fa	M	58		0	–	–	–	–	–	+	–	–	–	–	–	10	1.1
	1	F	22	21	m	–	+	–	+	–	+	+	+	+	+	–	22	40
	2	M	20		0	–	–	–	–	–	–	–	–	–	–	–	0	0.6
3	Fa	M	69		0	+	–	–	+	+	+	–	+	–	+	+	2.2	0.9
	Mo	F	53†	12	m	–	+	–	+	–	+	–	+	+	+	+		
	1	M	32		0	–	–	–	–	–	–	–	–	–	+	+	2.2	1.0
	P 2	F	30	26	m	–	+	+	+	–	+	+	+	–	+	+	20	38
	3	M	28		0	–	–	–	–	–	–	–	–	+	+	–	1.0	1.4
4	Fa	M	68		0	–	–	–	–	–	–	–	–	–	–	–	1.4	2.1
	Mo	F	68†			–	–	–	–	–	+	+	+	–	+			
	2	F	51		l	–	–	–	+	–	+	–	+	–	+	+	2.1	2.9
	3	M	48		l	–	–	–	–	–	–	–	–	–	+	–	16	33
	5	F	44	27	m	–	–	–	+	–	+	+	+	–	+	–	8	24
	P 6	F	40	20	m	+	–	–	+	+	+	+	+	+	+	–	7	14
	8	F	34	17	m	+	–	–	+	+	+	+	+	–	+	–	6	19

1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	19	19
5		Fa	M	64†			−	+	+	−	−	−	−	−	+	+			
		Mo	F	65†															
		3	F	54		l	−	−	−	−	−	−	−	−	−	+	+	1.1	5.1
	P	2	F	50	22	m	−	+	+	+	−	+	+	+	+	+	+	5.8	15
		3	M	49		0	−	−	−	−	−	−	−	−	−	−	−	2.7	0
		4	M	46		0	−	−	−	−	−	−	−	−	−	−	+	3.1	0.8
		5	M	42		l	−	−	−	−	−	−	−	−	−	−	−	13	34
		6	M	35		0	−	−	−	−	−	−	−	−	−	−	−	1.7	0.3
6A		Mo	F	72		0	−	−	−	−	−	−	−	−	−	−	−	1.8	0.8
		1	M	47		0	−	−	−	−	−	−	−	−	−	−	−	2.5	1.1
6B		Fa	M	59†	55	m	+	+	+	+	−	+	+	+	−	+	+		
		1	F	42	28	m	+	+	+	+	−	+	+	+	−	+	−	22	28
		2	F	40		0	−	−	−	−	−	−	−	−	−	+	−	0	1.8
	P	3	F	38	27	m	+	+	−	+	+	+	+	+	+	+	+	3.7	14
7		Fa	M	63		l	−	−	−	−	−	+	−	−	−	−	−	3.1	2.7
		Mo	F	64†		0	−	−	−	−	−	−	−	−	−	−	−		
		1	M	35		0	−	−	−	−	−	−	−	−	−	−	−	2.4	1.8
	P	3	F	25	21	m	−	+	−	+	+	+	+	+	+	+	+	11	17
8		Fa	M	73†			−			+	+	+	+	+	−	+			
		Mo	F	72		l	−	−	−	−	−	−	−	−	−	+	−	5.4	3.8
		1	F	51		l	−	−	−	−	−	+	−	−	−	+	+	20	24
		2	M	49		l	−	−	−	−	−	−	−	−	−	+	−	18	94
	P	3	F	48	39	m	+	−	−	+	+	+	−	+	−	+	+	19	39
		4	F	47		0	+	−	−	+	−	+	−	+	−	+	+	2.6	0.5
		5	M	45		l	−	−	−	−	−	+	−	+	−	+	+	1.8	3.7
		6	F	43		0	−	−	−	−	−	−	−	−	−	−	−	3.2	0.6
		7	F	42	38	m	+	+	+	+	−	+	+	+	+	+	−	0.4	47
		8	M	40	30	m	−	−	−	−	−	−	−	−	+	+	−	11	8
		9	F	39	32	m	+	−	−	+	+	+	+	+	−	+	−	12	23
		10	F	37		0	−	−	−	+	−	+	−	+	−	−	−	3.4	0.5
		11	M	35		l	−	−	−	+	−	+	−	+	−	+	+	4.5	4.6
		12	M	32		0	−	−	−	−	−	−	−	−	−	+	+	3.7	0.9
		13	F	30		l	−	−	−	−	−	−	−	−	−	−	−	11	15

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
9	Fa	M	83†	42	m	–	–	–	–	–	–	–	–	–	+	–		
	Mo	F	78		0	–	–	–	–	–	–	–	–	–	–	+	2.9	4.7
	1	M	57	25	m	–	+	+	+	–	+	+	+	+	+	+	17	28
	2	F	55		1	–	–	–	–	–	–	–	–	–	+	+	7	11
	3	M	43†	22	m	–	+	–	+	–	+	+	+	+	+	+		
P	4	F	50	22	m	–	+	+	+	–	+	+	+	+	+	+	7.3	16
	6	F	27†			–												
	7	M	44		0	–	–	–	–	–	–	–	–	–	+	+	2.1	0.3
	8	F	42		0	–	–	–	–	–	–	–	–	–	–	–	2.0	0.5
	9	M	36†	33	m	–	+	+	+	–	+	–	+	+	+	–		
	10	F	37		0	–	–	–	–	–	–	–	–	–	–	–	4.5	1.7
10	Fa	M	66†		0	–	–	–	–	–	–	–	–	+	–	+		
	Mo	F	57†			–	–	–	+	–	+	+	+	–	+			
P	1	F	39	19	m	+	+	+	+	–	+	+	+	+	+	+	2.7	3.7
	2	F	31		0	–	–	–	–	–	–	–	–	–	–	–	3.6	0.5
	3	M	26		0	–	–	–	–	–	–	–	–	–	–	–	1.9	0.8
11	Fa	M	66†		1	–	–	–	–	–	–	–	–	+	+			
	Mo	F	76†		0	+	+	–	+	–	+	+	+	–	–	+		
	2	F	59		1	–	–	–	–	–	–	–	–	–	–	+	2.1	3.8
	3	M	24†		1													
	4	M	55		0	+	+	–	+	+	+	+	+	–	+	+	1.6	0.6
	6	F	52	32	m	–	+	–	+	–	+	+	+	+	+	+	4.2	18
	7	F	50		1	+	+	–	+	–	+	+	+	+	+	–	3.2	4.4
P	8	F	47	29	m	+	+	+	+	+	+	+	+	–	+	+	12	15
12	Fa	M	65†		0	–												
	Mo	F	76	53	m	+	+	–	+	+	+	+	+	+	+	+	10	13
	1	F	20†	20	m	–	+	+	–	–	+	+	+	+	+	+		
	3	F	51	39	m	–	–	–	+	–	+	–	+	–	+	+	14	20
	5	M	43	35	m	–	+	+	+	–	+	+	+	+	+	+	15	44
P	6	F	41	12	m	–	+	–	+	+	+	+	+	+	+	+	3.7	9.2
13A	Mo	F	72		0	–	–	–	–	–	+	–	–	–	+	+	1.5	2.2
	1	F	53		0	–	–	–	–	–	–	–	–	–	–	–	1.9	1.7
13B	Fa	M	74		0	–	–	–	–	–	–	–	–	–	–	–	3.1	2.9
	1	M	47†		0	–	–	–	–	–	–	–	–	–	–	–		
P	2	M	46	40	m	+	+	–	+	–	+	+	+	+	+	+	3.9	5.8
	3	M	45		0	–	–	–	+	–	+	–	+	–	+	–	2.5	1.0
	4	F	43		0	–	–	–	–	–	–	–	–	–	–	+	1.0	1.6
	5	M	42		0	–	–	–	–	–	–	–	–	–	+	–	2.1	0.9

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
14	Fa	M	35†			—												
	Mo	F	59		1	−	−	−	−	−	−	−	−	−	−	−	2.8	3.8
	1	M	39		1	−	−	−	+	−	+	+	+	−	+	+	6.1	7.4
	P 2	M	38	21	m	+	+	+	+	−	+	+	+	+	+	+	10	28
	4	F	32	27	m	−	−	−	+	−	+	−	+	−	+	−	18	40
	5	F	30		1	−	−	−	+	−	+	+	+	−	−	−	2.2	2.1
15	Fa	M	77†		1	+	−	−	+	−	+	−	+	−	+	−		
	Mo	F	62†			−	−	−	−	−	−	−	−	−	−	−		
	1	M	43†	39	m	−	−	−	−	−	−	−	−	−	+			
	P 2	M	59	54	m	−	+	+	+	+	+	+	+	+	+	−	43	64
	3	F	57	52	m	−	−	−	−	−	−	−	+	−	+	−	1.5	4.1
	4	F	55	21	m	−	−	−	+	−	+	−	+	−	+	−	2.6	6.6
	5	F	54	32	m	−	−	−	−	−	−	−	+	−	+	−	3.5	4.0
	6	M	52		0	−	−	−	−	−	−	−	−	−	−	−	2.4	1.4
	7	M	50	27	m	−	−	−	+	−	+	−	+	−	+	−	17	39
16	Fa	M	92†		1	−												
	Mo	F	83†		0	−												
	2	M	63†		0	−	−	−	−	−	−	−	−	+	−	+		
	3	F	67		0	−	−	−	−	−	−	−	−	+	+	−	5.2	0.5
	5	F	61	39	m	−	−	−	−	−	−	−	−	+	+	−	5.1	23
	6	F	25†	25	m	−	+	−	−	−	+	+	−	+	+			
	7	M	56		0	−	−	−	−	−	+	−	−	−	−	−	2.1	1.0
	8	F	53		0	−	−	−	−	−	−	−	−	−	+	+	5.1	2.0
	9	M	50	21	m	−	−	−	−	−	+	−	+	−	+	−	18	38
	P 10	M	48	17	m	−	−	−	+	−	+	+	+	+	+	−	8.7	12
	11	F	44		0	+	+	−	+	+	+	+	+	−	+	+	4.1	2.4
17	Fa	M	65†		0	−			+		+		+					
	Mo	F	67	54	m	−	−	−	−	−	−	−	+	−	+	−	9.6	37
	1	M	45	24	m	+	−	−	+	−	+	+	+	−	+	−	2.9	5.1
	2	M	43		0	+	−	−	+	−	+	+	+	−	+	+	2.6	1.3
	3	F	41		0	−	−	−	+	−	+	−	+	−	−	−	2.6	0.9
	P 4	M	37	25	m	+	+	−	+	−	+	+	+	−	+	−	4.3	2.9
	5	M	35		0	+	+	−	+	−	+	+	+	−	−	+	1.8	1.2
	6	M	33	8	m	−	−	−	−	−	−	−	−	−	+	−	5.3	8.9
	7	F	29		0	+	−	−	+	−	+	+	+	−	+	+	1.4	1.7
	8	M	26		0	−	−	−	−	−	−	−	−	−	−	−	1.9	0.9

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
18	Fa	M	74†		0	–												
	Mo	F	56†	55	m	–												
	1	M	55		0	–	–	–	–	–	–	+	–	–	–	–	2.5	0.1
	2	M	53		0	–	–	–	–	–	–	+	–	–	–	–	0.8	0.1
	3	F	48		0	–	–	–	–	–	–	–	–	–	–	+	4.1	0.6
P	4	M	36	34	m	+	+	+	+	–	+	+	+	+	+	–	1.1	2.6
19	Fa	M	67†			–												
	Mo	F	81†			–	+	–	–	–	–	–	–	–	–			
	1	M	62		0	–	–	–	+	–	+	–	+	–	–	+	1.3	0.3
	3	M	59		0	–	–	–	–	–	–	–	–	–	–	–	1.4	1.4
	4	M	57		1	+	+	–	+	–	+	+	+	–	–		4.9	4.9
	5	F	55		0	–	–	–	+	+	+	+	+	+	+	+	1.9	0
	6	M	52		1	+	+	+	+	–	+	+	+	–	+	+	2.6	2.5
	7	M	50		1	–	–	–	–	–	–	–	–	–	+	–	6.3	5.2
	8	M	48	46	m	–	+	–	+	–	+	+	+	–	+	–	16	21
P	9	M	45	27	m	+	+	+	+	–	+	+	+	–	+	+	9.4	16
20	Fa	M	60		0	–	–	–	–	–	–	–	–	–	–	–	1.0	0.9
	Mo	F	56	35	m	–	+	+	+	–	+	+	+	–	+	+	6.4	12
P	1	M	33	32	m	–	+	–	+	–	+	+	+	+	+	+	8.0	18
	2	M	30		0	–	–	–	–	–	–	–	–	–	–	–	11	6
21A	Mo	F	59†	50	m													
	1	F	52†	40	m	–	–	–	–	–	–	–	–	+	+			
21B	Fa	M	67†		0	–	–	–	–	–	–	–	–	–	+			
	1	M	71	59	m	–	–	–	–	–	–	–	+	+	+	+	10	23
	2	M	19†			–												
	3	M	67	51	m	–	–	–	–	–	–	–	+	+	+	+	22	32
	4	F	65		0	–	–	–	–	–	–	–	–	–	–	–	1.3	0.7
	5	F	62		0	–	–	–	–	–	–	–	–	–	–	+	0.3	1.3
P	6	F	57	43	m	–	–	–	–	–	–	–	+	–	+	+	7.1	14
22	Fa	M	57†			–	–	–	–	–	–	–	–	–	+			
	Mo	F	39†															
	1	M	48		0	–	–	–	–	–	–	–	–	–	–	–	4.3	0.4
	2	M	46		0	–	–	–	–	–	–	–	–	–	–	+	3.9	1.4
	3	F	45		0	–	–	–	–	–	–	–	–	–	+	+	2.7	1.1
P	4	F	43	31	m	–	–	–	–	–	–	–	+	–	+	+	11	37
	5	M	42	19	m	–	–	–	–	–	+	–	–	–	+	+	9.5	21
	6	M	40		0	–	–	–	–	–	–	–	–	–	–	–	1.5	0
	7	M	39		1	–	–	–	–	–	–	–	–	–	+	+	26	28
	8	F	36		0	–	–	–	–	–	–	–	–	–	–	–	2.2	0.7

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	Fa	M	77†			–	–	–	–	–	–	–	–	–	–			
	Mo	F	55†			–	–	–	–	–	–	–	–	–	–			
	1	F	71		0	–	–	–	–	–	–	–	–	–	+	–	1.9	0.4
	2	M	69		0	–	–	–	–	–	–	–	–	–	–	–	1.2	0.8
	3	M	66		0	–	–	–	–	–	–	–	–	–	–	+	2.8	1.3
23	4	M	64		0	–	–	–	–	–	–	–	–	–	+	+	2.1	0.5
	5	F	62		1	–	–	–	–	–	–	–	–	–	–	–	35	77
	6	F	61		0	–	–	–	–	–	–	–	–	–	–	–	4.1	1.3
	7	M	29†															
	8	M	56		0	–	–	–	–	–	–	–	–	–	–	–	3.0	1.1
	9	F	25†			–												
P	10	F	51	50	m	–	–	–	–	–	–	–	–	–	+	+	33	63
	Fa	M	64†		1	–	–	–	–	–	–	–	–	–	+	+		
	Mo	F	64		0	+	+	+	+	–	+	+	+	–	+	+	2.2	1.9
24	1	M	39		1	–	–	–	–	–	–	–	–	+	+	+	4.4	3.6
	2	M	37		1	+	+	+	+	–	+	+	+	+	+	+	3.8	4.0
P	3	F	32	16	m	–	–	–	–	–	–	–	–	–	+	–	9.5	39
	Fa	M	63†		1	–	–	–	–	–	–	–	–	–	+	–		
	Mo	F	73†		0	–	–	–				–	–					
	1	M	61		0	–	–	–	–	–	–	–	–	–	–	–	4.5	1.9
	2	F	59	21	m	–	–	–	–	–	+	–	+	+	+	+	7.9	31
	3	F	57		0	–	–	–	–	–	–	–	–	–	–	–	3.2	1.8
	4	M	55		0	–	–	–	–	–	–	–	–	–	–	–	3.9	0.8
	5	M	53	34	m	–	+	+	+	–	+	+	+	+	+		23	75
25	6	M	51		1	–	–	–	–	–	–	–	–	–	+	+	97	15
	7	F	48		0	–	–	–	–	–	–	–	–	–	–	–	2.9	1.2
P	8	F	46	41	m	–	–	–	–	–	–	–	–	–	+	–	13	34
	9	M	42		1	–	–	–	–	–	–	–	–	–	–	+	7.6	7.8
	10	M	39		1	–	–	–	–	–	–	–	+	–	+	+	2.6	3.0
	11	M	35		1	–	–	–	–	–	–	–	–	–	–	–	2.9	74
	12	M	33		1	–	–	–	–	–	–	–	+	–	–	–	2.1	3.1
	13	M	33		0	–	–	–	–	–	–	–	–	–	–	–	2.7	0.5
	Fa	M	51		0	–	–	–	–	–	–	–	–	–	–	–	2.9	1.2
	Mo	F	48		1	+	–	–	+	–	+	–	+	–	–	+	3.6	2.6
26	1	M	25		1	–	–	–	–	–	–	–	–	–	+	–	13	11
P	2	F	24	21	m	–	–	–	–	–	–	–	–	–	+	+	2.9	4.2
	3	F	19		0	–	–	–	–	–	–	–	–	–	–	–	1.9	2.5

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	Fa	M	70†			–	–	–	–	–	–	–	–	–	+			
	Mo	F	85†			–	–	–	–	–	–	–	–	–	–			
27	1	M	60	52	m	–	–	–	+	–	+	+	+	–	+	+	5.4	3.5
P	2	F	59	47	m	–	–	–	–	–	–	–	–	–	+	–	8.1	10
	3	F	36†	36	m									+	+			
	4	F	57	35	m	+	+	+	+	–	+	+	+	+	+	+	7.8	14
	6	F	54		0	–	–	–	–	–	–	–	–	–	–	–	3.7	1.7
	Fa	M	77†		1	–	–	–	–	–	–	–	–					
	Mo	F	78†		0	–	–	–	–	–	–	–	–	–	–			
	1	F	70	60	m	–	–	–	+	+	+	–	+	–	+	+	4.8	11
	2	M	69†		0	–	–	–	–	–	–	–	–	–	+			
	3	M	67		1	–	–	–	–	–	–	–	–	+	+	–	0.9	8.2
28	4	F	65	40	m	–	+	–	+	+	+	+	+	+	+	+	7.6	12
	5	F	53†		0	–	–	–	–	–	–	–	–	–	+	+		
	6	F	56†		0	+	+	+	+	–	+	–	+	+	–	+		
P	7	F	59	40	m	–	–	–	–	–	–	–	–	–	+	–	5.7	6.6
	8	F	57		0	–	–	–	+	–	+	–	+	–	+	+	1.5	0
	9	F	55		1	–	–	–	–	–	–	–	–	+	+	–	2.4	3.3
	Fa	M	54†			–									+			
	Mo	F	33†			–	+	–	–	–	+	+	+	+	–			
29A	1	F	37	20	m	–	–	–	–	–	–	–	–	–	+	–	2.5	7.4
P	2	F	34	19	m	–	–	–	–	–	–	–	–	–	+	–	11	14
	Mo	F	49		0	–	–	–	–	–	–	–	–	–	–	+	0.9	0.8
29B	2	M	28		0	–	–	–	–	–	–	–	–	–	+	–	2.8	1.5
	3	F	23		0	–	–	–	–	–	–	–	–	–	–	–		
	Fa	M	67		0	–	–	–	–	–	–	–	–	–	–	–	2	0.7
	Mo	F	69†	66	m	+	+	+	+	–	+	+	+	+	+	+		
30	1	M	48		1	–	–	–	–	–	–	–	–	–	–	–	19	24
P	2	F	44	35	m	–	–	–	–	–	–	–	–	+	+	+	12	24
	Fa	M	58		0	–	–	–	–	–	–	–	–	–	–	–	0	0.2
	Mo	F	61	39	m	–	–	–	–	–	–	–	–	+	+	–	5.1	23
31	1	M	32		0	–	–	–	–	–	–	–	–	–	–	–	1.4	2.1
	2	F	31	15	m	–	+	–	–	–	+	+	+	+	+	–	20	46
	3	F	30		0	–	–	–	–	–	+	–	–	–	–	–	0.2	2.4
P	4	F	22	18	m	–	–	–	–	–	–	–	+	–	+	–	25	73

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
32	Fa	M	62		0	–	–	–	–	–	–	–	–	–	–	+	3.3	1.7
	Mo	F	54		1	–	–	–	–	–	–	–	–	–	+	+	1.8	5.1
	1	M	36		0	–	–	–	–	–	–	–	–	–	+	–	1.5	0.8
	2	M	34		0	–	–	–	–	–	–	–	–	–	–	+	1.6	0.6
	P 3	M	32	31	m	–	–	–	–	–	–	–	–	–	+	–	17	27
	4	M	29		0	–	–	–	–	–	–	–	–	–	+	+	2.4	0.5
	5	M	18		0	–	–	–	–	–	–	–	–	–	–	+	1.7	0.7
33	Fa	M	82†			–	–	–	–	–	–	–	–	–	+			
	Mo	F	46†															
	1	M	58†		m	+	+	–	+	+	+	–	+	–	+			
	2	M	62		0	–	–	–	–	–	–	–	–	–	–	+	2.5	0
	3	F	60	57	m	–	+	–	–	–	–	–	–	+	+	+	25	35
	P 4	M	58	24	m	–	–	–	–	–	–	–	+	–	+	–	17	39
	6	F	19†	19	m	+	–	–	+	–	+	–	+	+	+	+		
	7	M	51		0	–	–	–	–	–	–	–	–	–	+	+	2.4	0
	8	F	23†	19	m	–	+	–	–	–	–	–	–	+	+	+		
34	Fa	M	78†		1	–	–	–	–	–	–	–	–	–	–			
	Mo	F	63†			–	–	–	–	–	–	–	–	–	+	+		
	1	M	70		0	–	–	+	–	–	+	+	+	–	–	+	2	0.5
	P 2	M	68	34	m	–	–	–	–	–	–	–	–	+	+	+	12	18
	3	F	64		0	–	–	–	–	–	–	–	–	–	–	–	2.4	0.8
	4	M	61		0	–	–	–	–	–	–	–	–	–	+	+	4.1	2.6
	5	F	59		0	–	–	–	–	–	–	–	–	–	+	–	2.5	3.0
	6	F	57	35	m	–	–	–	–	–	+	–	–	–	+	+	22	46
35	Fa	M	47†		m	–	–	–	–	–	+	–	+	–	+	–		
	Mo	F	56		0	–	–	–	–	–	–	–	–	–	–	–	7.1	0.6
	P 1	M	32	30	m	–	–	–	–	–	–	–	–	+	+	–	43	86
	2	M	22		1	–	–	–	–	–	–	–	+	–	–	–	16	38
	3	F	19		0	–	–	–	–	–	–	–	–	–	–	–	1.1	0.9
36	Fa	M	41†		m	–												
	Mo	F	49		0	–	–	–	–	–	–	–	–	–	–	–	3	0.7
	1	M	29		0	–	–	–	–	–	–	–	–	–	–	–	0.6	0
	P 2	M	27	25	m	–	–	–	–	–	–	–	+	–	+	+	17	20
	3	M	22		0	–	–	–	–	–	–	–	–	–	+	–	0.7	2.6
	4	F	21	17	m	+	+	+	+	–	+	+	+	+	+	+	60	110
	5	M	19	19	m	–	–	–	–	–	–	–	–	–	+	–	48	49

1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
37		Fa	M	74†			–	–	–	–	–	–	–	–	–	+			
		Mo	F	56†			–	–	–	–	–	–	–	–	–	+			
		1	M	44†	42	m	–									+			
		3	F	67		0	–	–	–	–	–	–	–	–	–	–	+	2.3	0.8
		4	F	34†	34	m	–	–	–	–	–	–	–	–	–	+	+		
		5	M	36†	36	m	–	+	–	–	–	+	+	+	+	+	+		
	P	6	M	61	38	m	–	–	–	–	–	–	+	–	+	+	–	6.2	3.2
		7	F	59		0	–	–	–	–	–	–	–	–	–	–	–	2.3	1.1
		8	M	56		0	–	–	–	–	–	–	–	–	–	–	+	1.6	1.3
38		Fa	M	54		0	–	–	–	–	–	–	–	–	–	–	–	2.4	0.6
		Mo	F	46		1	–	–	–	+	–	+	–	+	–	+	–	6.8	4.3
	P	1	M	27	23	m	–	–	–	–	–	–	–	+	–	+	–	16	38
		2	M	26		0	–	–	–	–	–	–	–	–	–	–	–	2.2	0.3
		3	M	21		0	–	–	–	–	–	–	–	–	–	–	–	2.4	0.7
		4	M	13		0	–	–	–	–	–	–	–	–	–	+	–	9.4	1.0
39		Fa	M	51†			–												
		Mo	F	79†			–	–	–	–	–	–	–	–	–	+			
		2	F	48		1	–	–	–	–	–	–	–	–	–	+	–	5.0	3.8
	P	3	M	46	37	m	–	–	–	–	–	–	–	+	–	+	+	8.5	6.9
40A		Mo	F	66†			–	–	–	–	–	+	–	+	–	–			
		1	F	44		0	–	–	–	+	–	+	–	+	–	–	+	2.0	0.5
40B		Fa	M	30†			–	–	–	–	–	–	–	–					
	P	1	M	42	39	m	–	–	–	–	–	–	–	–	+	+	–	40	36
		2	F	24†	23	m	+	+	+	+	+	+	+	+	+	+	+		
		3	M	38		0	–	–	–	–	–	–	–	–	–	–	+	1.3	0.3
40C		1	F	29		0	–	–	–	–	–	–	–	–	–	–	–	2.7	0.8

Acute intermittent porphyria (AIP), inherited as an autosomal dominant gene is characterized by abdominal, neurological and psychiatric symptoms.

The major problem in this work concerns the association between AIP and mental illness. A specially designed genetical analysis of a randomly selected sample of 40 families provides evidence for or against different hypotheses to explain such associations.

The conclusion is that there is a likelihood of a genuine AIP mental syndrome, which should be suspected when the following signs or symptoms are present: slight to moderate depression, transitional confusion, frequently visual hallucinations and neurological signs.